PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrCERDELGA™

Eliglustat capsules

Capsule, 84 mg eliglustat (as eliglustat tartrate), for oral administration

Various Alimentary Tract and Metabolism Product

sanofi-aventis Canada Inc.

1755 Steeles Avenue West

Toronto, ON

M2R 3T4

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RECENT MAJOR LABEL CHANGES

Not Applicable

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CERDELGA (eliglustat) is indicated for:

- the long-term treatment of adult patients with Gaucher disease type 1 (GD1) who are CYP2D6 poor metabolizers (PMs), intermediate metabolizers (IMs) or extensive metabolizers (EMs), as determined by CYP2D6 genotype testing.

Limitations of Use

CERDELGA should not be used in patients genotyped as:

- CYP2D6 ultra-rapid metabolizers (URMs) as these patients may not achieve adequate concentrations of CERDELGA to achieve a therapeutic effect
- CYP2D6 indeterminate metabolizers as a specific dosage cannot be recommended for these patients

1.1 Pediatrics

Pediatrics (< 18 years of age): Safety and effectiveness in pediatric patients have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): A limited number of patients aged 65 years and over were enrolled in clinical trials. As greater rates of hepatic, renal, and cardiac function impairment are observed in elderly patients, this patient population may be more sensitive to the effects of CERDELGA (see 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

2 CONTRAINDICATIONS

CERDELGA is contraindicated in patients (all CYP2D6 metabolizer types) with:

- Hypersensitivities to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the product monograph
- Rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption

CERDELGA is contraindicated in the following patients based on CYP2D6 metabolizer status due to the risk of significantly increased eliglustat plasma concentrations, which may increase the risk of cardiac arrhythmias from prolongation of the PR, QTc and/or QRS cardiac intervals (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular):

EMs

- Taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor (see 9 DRUG INTERACTIONS)
- Mild hepatic impairment and taking a strong or moderate CYP2D6 inhibitor (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, 4 DOSAGE AND ADMINISTRATION and 10

CLINICAL PHARMACOLOGY)

- Mild hepatic impairment taking a strong CYP3A inhibitor (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic,4 DOSAGE AND ADMINISTRATION and10 CLINICAL PHARMACOLOGY)
- Moderate or severe hepatic impairment (see7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic)

IMs

- Taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor (see9 DRUG INTERACTIONS)
- Taking a strong CYP3A inhibitor (see7 WARNINGS AND PRECAUTIONS, Cardiovascular and 9 DRUG INTERACTIONS)
- Any degree of hepatic impairment (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY)

PMs

- Taking a strong CYP3A inhibitor (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 9 DRUG INTERACTIONS)
- Any degree of hepatic impairment (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Therapy with CERDELGA should be initiated and supervised by a physician knowledgeable in the management of Gaucher disease.

Before initiation of treatment with CERDELGA, patients must be genotyped for CYP2D6 to determine the CYP2D6 metabolizer status (predicted phenotype). CERDELGA is indicated for patients who are CYP2D6 PMs, IMs or EMs, as determined by CYP2D6 genotype testing (see 1 INDICATIONS).

CERDELGA should not be used in patients who are CYP2D6 URMs or indeterminate metabolizers (see 1 INDICATIONS, Limitations of use).

For patients currently treated with imiglucerase, velaglucerase alfa, or taliglucerase alfa, CERDELGA may be administered 24 hours after the last dose of the previous ERT.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of CERDELGA depends on CYP2D6 metabolizer status, as follows:

- CYP2D6 Extensive metabolizer (EM): CERDELGA dosage is 84 mg twice daily
- CYP2D6 Intermediate metabolizer (IM): CERDELGA dosage is 84 mg twice daily
- CYP2D6 Poor metabolizer (PM): CERDELGA dosage is 84 mg once daily

The recommended dose of CERDELGA also depends on concomitant medication use as well as hepatic and renal impairment as follows in **Table 1**, **Table 2** and **Table 3** (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, 7 WARNINGS AND PRECAUTIONS, Renal and 9 DRUG INTERACTIONS):

Table 1 – Dosing Recommendations for CERDELGA Due to Drug-Drug Interactions with CYP Inhibitors and Inducers in CYP2D6 Extensive Metabolizers, Intermediate Metabolizers and Poor Metabolizers.

<table>
<tr><th rowspan="2">Concomitant Drug Class: Drug Name</th><th colspan="3">Dosing Recommendations</th></tr>
<tr><th>Extensive Metabolizers (EMs)</th><th>Intermediate Metabolizers (IMs)</th><th>Poor Metabolizers (PMs)</th></tr>
<tr><td>Strong CYP3A Inhibitors used concomitantly with Strong/Moderate CYP2D6 Inhibitors (e.g., ketoconazole+ paroxetine/terbinafine)</td><td rowspan="2">Contraindicated</td><td rowspan="2">Contraindicated</td><td>Contraindicated</td></tr>
<tr><td>Moderate CYP3A Inhibitors used concomitantly with Strong/ Moderate CYP2D6 Inhibitors
(e.g., fluconazole+paroxetine/ terbinafine)</td><td>Not recommended</td></tr>
<tr><td>Strong CYP2D6 Inhibitors (e.g., paroxetine, fluoxetine, quinidine, bupropion)</td><td>Not recommended</td><td>Not recommended</td><td>84 mg CERDELGA once daily</td></tr>
<tr><td>Moderate CYP2D6 Inhibitors (e.g., terbinafine, duloxetine, moclobemide, mirabegron, cinacalcet, dronedarone)</td><td>84 mg CERDELGA once daily</td><td>84 mg CERDELGA once daily</td><td>84 mg CERDELGA once daily</td></tr>
<tr><td>Weak CYP2D6 Inhibitors
(e.g. abiraterone, amiodarone, celecoxib, cimetidine, clobazam, cobicistat, desvenlafaxine, escitalopram, labetalol, lorcaserin, ritonavir, sertraline, vemurafenib)</td><td>84 mg CERDELGA twice daily</td><td>No data available[a]</td><td>84 mg CERDELGA once daily</td></tr>
</table>

Concomitant Drug Class: Drug Name	Dosing Recommendations		
	Extensive Metabolizers (EMs)	Intermediate Metabolizers (IMs)	Poor Metabolizers (PMs)
Strong CYP3A Inhibitors (e.g., ketoconazole, clarithromycin, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, conivaptan, boceprevir)	84 mg CERDELGA once daily	Contraindicated	Contraindicated
Moderate CYP3A Inhibitors (e.g., fluconazole, erythromycin, ciprofloxacin, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine)	84 mg CERDELGA once daily	84 mg CERDELGA once daily	Not recommended
Weak CYP3A Inhibitors (e.g., ranitidine, amlopidine, fluvoxamine, goldenseal, isoniazid)	84 mg CERDELGA twice daily	No data available[a]	Not recommended
Strong CYP3A Inducers (e.g. rifampin, carbamazepine, phenobarbital, phenytoin, rifabutin)	Not recommended	Not recommended	Not recommended

[a]No clinical data provided to make a dosing recommendation

Table 2 – Recommended Dose for CERDELGA Based on Presence and Severity of Hepatic and Renal Impairment Status by CYP2D6 Metabolizer Status

Organ Dysfunction status	Dosing Recommendations		
	Extensive Metabolizers (EMs)	Intermediate Metabolizers (IMs)	Poor Metabolizers (PMs)
Hepatic impairment status: Without hepatic impairment	84 mg CERDELGA twice daily	84 mg CERDELGA twice daily	84 mg CERDELGA once daily

Organ Dysfunction status	Dosing Recommendations		
	Extensive Metabolizers (EMs)	**Intermediate Metabolizers (IMs)**	**Poor Metabolizers (PMs)**
Mild Hepatic Impairment (Child-Pugh Class A)	84 mg CERDELGA once daily	Contraindicated	Contraindicated
Moderate or Severe Hepatic Impairment (Child-Pugh Class B or C)	Contraindicated	Contraindicated	Contraindicated
Renal impairment status (creatinine clearance [CrCl]): Without renal impairment (eCrCl >80 mL/min)	84 mg CERDELGA twice daily	84 mg CERDELGA twice daily	84 mg CERDELGA once daily
Mild, Moderate or Severe Renal Impairment (eCrCl: ≥15-≤80 ml/min)	84 mg CERDELGA twice daily	Not recommended	Not recommended
End stage renal disease (ESRD) (eCrCl: <15 ml/min)	Not recommended	Not recommended	Not recommended

Table 3– Dosing Recommendations for CERDELGA in Mild Hepatic Impaired Patients Due to Drug-Drug Interactions in CYP2D6 Extensive Metabolizers

Mild Hepatic Impairment+ Concomitant Drug Class: Drug Name	Dosing Recommendations
	Extensive Metabolizers (EMs)
Mild hepatic impairment + Strong CYP2D6 Inhibitors (e.g., paroxetine, fluoxetine, quinidine, bupropion)	Contraindicated
Mild hepatic impairment + Moderate CYP2D6 Inhibitors (e.g., terbinafine, duloxetine, moclobemide, mirabegron, cinacalcet, dronedarone)	Contraindicated
Mild hepatic impairment + Weak CYP2D6 Inhibitors (e.g., ritonavir)	84 mg CERDELGA once daily
Mild hepatic impairment+Strong CYP3A Inhibitors (e.g., ketoconazole, clarithromycin, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir,	Contraindicated

Mild Hepatic Impairment+ Concomitant Drug Class: Drug Name	Dosing Recommendations
	Extensive Metabolizers (EMs)
telaprevir, tipranavir, posaconazole, voriconazole, conivaptan, boceprevir)	
Mild hepatic impairment+Moderate CYP3A Inhibitors (e.g., fluconazole, erythromycin, ciprofloxacin, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine)	84 mg CERDELGA once daily
Mild hepatic impairment+Weak CYP3A Inhibitors (e.g., ranitidine, amlopidine, fluvoxamine, goldenseal, isoniazid)	84 mg CERDELGA once daily

For additional information regarding CERDELGA hepatic and renal impairment and drug interactions, see 10 CLNICAL PHARMACOLOGY, Pharmacokinetics: Special Populations and Conditions

and Table 9, Table 10 and Table 11.

Geriatrics (≥65 years of age): A limited number of patients aged 65 and over were enrolled in clinical trials. As greater rates of hepatic, renal, and cardiac function impairment are observed in elderly patients, this patient population may be more sensitive to the effects of CERDELGA. Use with caution (see 7 WARNINGS AND PRECAUTIONS and 10.3Pharmacokinetics, Special Populations and Conditions

, Geriatrics).

4.4 Administration

Swallow capsules whole, preferably with water, and do not crush, dissolve, or open the capsules. CERDELGA can be taken with or without food. Consumption of grapefruit or its juice should be avoided (see 9.5 Drug-Food Interactions)

4.5 Missed Dose

If a dose of CERDELGA is missed, take the prescribed dose at the next scheduled time; do not double the next dose.

5 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 (e.g., ECG monitoring) and given symptomatic and supportive treatment.

Hemodialysis is unlikely to be beneficial given that CERDELGA has a large volume of distribution (see 10 CLINICAL PHARMACOLOGY).

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsule 84 mg eliglustat, as eliglustat tartrate	Each capsule contains 111.5 mg lactose (as monohydrate).

CERDELGA 84 mg capsule for oral administration contains the following excipients: glyceryl behenate/glycerol dibehenate, hypromellose, lactose monohydrate, microcrystalline cellulose. The capsule shell is composed of gelatin, candurin silver fine, yellow iron oxide (E172) and indigotine (E132). In the printing ink: shellac glaze, black iron oxide (E172), propylene glycol, potassium aluminum silicate (E555) and ammonium hydroxide 28%.

CERDELGA is supplied as 84 mg hard gelatin capsules, with a blue-green opaque cap and white opaque body imprinted with “GZ02” in black. Each 84 mg capsule of CERDELGA is equivalent to 100 mg of eliglustat tartrate (hemitartrate salt).

CERDELGA 84 mg capsules are supplied as:

- Carton of 14 capsules containing 1 pack (i.e., 1 inner carton). Each pack is composed of 1 blister card of 14 capsules and a cardboard wallet.

- Carton of 56 capsules containing 4 packs (i.e., 4 inner cartons). Each pack is composed of 1 blister card of 14 capsules and a cardboard wallet.

Not all pack sizes may be marketed.

7 WARNINGS AND PRECAUTIONS

General

Drug-drug interactions

CERDELGA is a CYP2D6 and CYP3A substrate. Drugs that inhibit CYP2D6 and CYP3A metabolism pathways can significantly increase the exposure to eliglustat, which has the potential to lead to

prolongation of the PR, QTc, and/or QRS ECG intervals and possibly result in cardiac arrhythmias (see 10 CLINICAL PHARMACOLOGY).

CERDELGA is contraindicated in patients who are CYP2D6 IMs or EMs, taking a strong (e.g., paroxetine, fluoxetine, quinidine) or moderate (e.g. duloxetine, terbinafine) CYP2D6 inhibitor concomitantly with a strong (e.g., clarithromycin, itraconazole) or moderate (e.g., erythromycin, fluconazole) CYP3A inhibitor, and in patients who are CYP2D6 PMs or IMs, taking a strong CYP3A inhibitor. Under these conditions both major metabolic pathways for CERDELGA metabolism are impaired, with predicted substantially elevated eliglustat plasma concentrations (see 2 CONTRAINIDCATIONS, 7 WARNINGS AND PRECAUTIONS, Cardiovascular , 4 DOSAGE AND ADMINISTRATION and 9 DRUG INTERACTIONS).

Cerdelga is not recommended in EMs, IMs, or PMs when co-administered with certain CYP2D6 and/or CYP3A inhibitors (see 4 DOSAGE AND ADMINISTRATION and 9 DRUG INTERACTIONS).

Use of CERDELGA with strong CYP3A inducers substantially decreases the exposure to CERDELGA, which may reduce the therapeutic effectiveness of CERDELGA; therefore, concomitant administration is not recommended (see 9 DRUG INTERACTIONS and 4 DOSAGE AND ADMINISTRATION).

Cardiovascular

Electrocardiogram (ECG) Changes and Potential for Cardiac Arrhythmias

CERDELGA is predicted to cause concentration-related increases in ECG intervals (PR, QTc, and QRS) (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, 9 DRUG INTERACTIONS**,** and 10 CLINICAL PHARMACOLOGY, Electrocardiographic evaluation. Use of CERDELGA is not recommended in patients with pre-existing cardiac disease (e.g., congestive heart failure, ischemic heart disease, recent acute myocardial infarction, bradycardia, heart block, atrial or ventricular arrhythmia, long QT syndrome, presence of pathologic genetic variants affecting cardiac ion channels or regulatory proteins), electrolyte disturbances, (e.g., hypokalemia, hypomagnesemia, hypocalcemia) or conditions that can lead to electrolyte disturbances (e.g. eating disorders) and in combination with Class IA (e.g., quinidine, procainamide), Class IC (flecainide, propafenone) and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications. Caution is recommended in patients with a history of syncope or a family history of sudden cardiac death at <50 years. Non-sustained supraventricular and ventricular arrhythmias, as well as second degree atrioventricular blocks (Mobitz I), were observed in clinical trials.

Use of CERDELGA in patients with pre-existing cardiac conditions has not been studied during clinical trials.

Hepatic/Biliary/Pancreatic

Use of CERDELGA in patients with hepatic impairment as well as with concomitant CYP2D6 or CYP3A inhibitors can result in elevation of eliglustat plasma concentrations, with the magnitude of the effect depending on the degree of hepatic impairment, as well as the enzyme inhibited and the potency of the inhibitor (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 10 CLINICAL PHARMACOLOGY, Pharmacokinetics and Special Populations and Conditions

)).

Based on CYP2D6 metabolizer status and under conditions of hepatic impairment and/or concomitant use of CYP2D6 or CYP3A inhibitors, CERDELGA is contraindicated or recommended for a dose reduction as follows:

EMs

- CERDELGA is contraindicated in patients with (see 2 CONTRAINDICATIONS):
    - Severe (Child-Pugh Class C) hepatic impairment
    - Moderate (Child-Pugh Class B) hepatic impairment
    - Mild (Child-Pugh Class A) hepatic impairment taking a strong or moderate CYP2D6 inhibitor or a strong CYP3A inhibitor

- A dosage adjustment is recommended in patients with mild hepatic impairment (see 4 DOSAGE AND ADMINISTRATION)

IMs and PMs:

- CERDELGA is contraindicated in patients with any degree of hepatic impairment (see 2 CONTRAINDICATIONS).

Monitoring and Laboratory Tests

CYP2D6 metabolizer status

Before initiation of treatment with CERDELGA, patients must be genotyped for CYP2D6 to determine their CYP2D6 metabolizer status (predicted phenotype) (see 1 INDICATIONS and 4 DOSAGE AND ADMINISTRATION).

Electrocardiogram

If CERDELGA is administered to patients with baseline ECG abnormalities which might be exacerbated by the QTc, QRS, or PR interval prolonging effects of the drug, then ECG monitoring during treatment should be performed as clinically indicated.

ECG monitoring should also be considered if CERDELGA is used concomitantly with other QTc-, QRS-, or PR-interval prolonging drugs (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 9 DRUG INTERACTIONS).

Renal

Use of CERDELGA in patients with renal impairment is based on the patient's CYP2D6 metabolizer status as follows (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY, Pharmacokinetics):

EMs:

- CERDELGA is not recommended in patients with end stage renal disease (ESRD) (estimated creatinine clearance less than 15 mL/min not on dialysis or requiring dialysis)

- No dosage adjustment is recommended in patients with mild, moderate or severe renal impairment (estimated creatinine clearance 15 mL/min or higher)

IMs and PMs:

- CERDELGA is not recommended in patients with any degree of renal impairment

7.1 Special Populations

Ultra-rapid metabolizers and indeterminate metabolizers:
CERDELGA should not be used in patients who are CYP2D6 URMs or indeterminate metabolizers (see 1 INDICATIONS).

7.1.1 Pregnant Women

There are no adequate or well-conducted studies with CERDELGA in pregnant women. Placental transfer of eliglustat and/or its metabolites were detected at trace amounts in nonclinical studies. Eliglustat displayed embryo/fetal toxicity in animal studies at high doses and exposures that were associated with maternal toxicity (see 16 NON-CLINICAL TOXICOLOGY). Avoid the use of CERDELGA during pregnancy.

7.1.2 Breast-feeding

In non-clinical studies, eliglustat has been shown to pass in trace amounts into breast milk (see 16 NON-CLINICAL TOXICOLOGY). It is not known whether CERDELGA is present in human milk. Because of the potential for serious adverse reactions from CERDELGA in nursing infants, 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.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age):
There were a limited number of patients aged 65 and over enrolled in clinical trials. As greater rates of hepatic, renal, and cardiac function impairment are observed in elderly patients, this patient population may be more sensitive to the effects of CERDELGA. Use with caution (see 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Based on the initial pooled clinical trial data representing 535 patient-years of treatment exposure in 393 adult patients, the most commonly reported adverse reactions with CERDELGA (occurring in ≥5% of patients) were headache and dizziness. The most frequently reported serious adverse event was

syncope (1%). The most common adverse events leading to discontinuation of CERDELGA and/or withdrawal from the studies were ventricular tachycardia (1%) and (acute) myocardial infarction (1%).

8.2 Clinical Trial Adverse Reactions

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

The adverse reaction profile of CERDELGA is based on two controlled studies, ENGAGE (GZGD02507) and ENCORE (GZGD02607). **Table 4** presents adverse reactions in patients receiving CERDELGA in the 9-month double-blind, randomized, placebo-controlled trial of 40 treatment-naïve patients (ENGAGE). 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 4 - Summary of Treatment-Emergent Adverse Reactions (considered treatment-related by Investigator) in Treatment-Naïve Gaucher Disease Type 1 Patients receiving CERDELGA as compared to Patients receiving Placebo (ENGAGE Trial)

Adverse Reaction **MedDRA System Organ Class** Preferred Term	**CERDELGA (N=20)** **Patients n (%)**	**Placebo (N=20)** **Patients n (%)**
Gastrointestinal disorders		
Diarrhea	2 (10)	4 (20)
Abdominal pain	1 (5)	2 (10)
Flatulence	2 (10)	1 (5)
Gastritis	1 (5)	0 (0)
Nausea	1 (5)	0 (0)
Vomiting	1 (5)	0 (0)
Nervous system disorders		
Headache	1 (5)	3 (15)
Paresthesia	1 (5)	0 (0)
Skin and subcutaneous tissue disorders		
Acne	1 (5)	0 (0)
Skin lesion	1 (5)	0 (0)
Eye disorders		
Vitreous detachment	1 (5)	0 (0)
General disorders and administration site conditions		
Chest pain	1 (5)	0 (0)
Edema peripheral	1 (5)	0 (0)
Metabolism and nutrition disorders		
Decreased appetite	1 (5)	1 (5)
Blood and lymphatic system disorders		

Adverse Reaction **MedDRA System Organ Class** Preferred Term	**CERDELGA (N=20)**	**Placebo (N=20)**
	Patients n (%)	**Patients n (%)**
Splenic hemorrhage	1 (5)	0 (0)
Infections and infestations		
Oral fungal infection	1 (5)	0 (0)
Musculoskeletal and connective tissue disorders		
Arthralgia	1 (5)	0 (0)
Renal and urinary disorders		
Dysuria	1 (5)	0 (0)
Hematuria	1 (5)	0 (0)

Error! Reference source not found. presents adverse reactions in patients receiving CERDELGA in the 12-month open-label, randomized, CEREZYME® controlled trial of 159 patients previously treated with enzyme replacement therapy (ERT), randomized 2:1 to receive CERDELGA or CEREZYME® (ENCORE Trial). 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 5 - Summary of Treatment-Emergent Adverse Reactions (considered treatment-related by Investigator) in Gaucher Disease Type 1 Patients Switching from Enzyme Replacement Therapy to CERDELGA as compared to Patients receiving CEREZYME® (ENCORE Trial)

Adverse Reaction **MedDRA System Organ Class** Preferred Term	**CERDELGA (N=106)** **Patients n (%)**	**CEREZYME® (N=53)** **Patients n (%)**
Gastrointestinal disorders		
Diarrhea	5 (5)	0 (0)
Dyspepsia	3 (3)	1 (2)
Gastroesophageal reflux disease	3 (3)	0 (0)
Nausea	3 (3)	0 (0)
Abdominal pain upper	2 (2)	0 (0)
Constipation	2 (2)	0 (0)
Dry mouth	2 (2)	0 (0)
Dysphagia	2 (2)	0 (0)
Flatulence	2 (2)	0 (0)
Abdominal distension	1 (1)	0 (0)
Abdominal pain	1 (1)	0 (0)
Eructation	1 (1)	0 (0)
Gastritis	1 (1)	0 (0)
Glossodynia	1 (1)	0 (0)
Esophageal pain	1 (1)	0 (0)
Nervous system disorders		
Headache	4 (4)	0 (0)
Somnolence	3 (3)	0 (0)
Dizziness	2 (2)	0 (0)
Tremor	2 (2)	0 (0)
Dysgeusia	1 (1)	0 (0)
Hypoesthesia	1 (1)	0 (0)
Hyposmia	1 (1)	0 (0)
Neuropathy peripheral	1 (1)	0 (0)
Paresthesia	1 (1)	0 (0)
Parosmia	1 (1)	0 (0)
General disorders and administration site conditions		
Fatigue	4 (4)	0 (0)
Asthenia	2 (2)	0 (0)
Chest pain	1 (1)	0 (0)
Thirst	1 (1)	0 (0)
Musculoskeletal and connective tissue disorders		
Arthralgia	4 (4)	0 (0)
Back pain	1 (1)	1 (2)

Adverse Reaction **MedDRA System Organ Class** Preferred Term	**CERDELGA (N=106)** **Patients n (%)**	**CEREZYME® (N=53)** **Patients n (%)**
Pain in extremity	2 (2)	0 (0)
Bone pain	1 (1)	0 (0)
Tendon disorder	1 (1)	0 (0)
Investigations		
Blood folate decreased	2 (2)	0 (0)
Blood homocysteine increased	2 (2)	0 (0)
Mean cell hemoglobin increased	1 (1)	0 (0)
Nerve conduction studies abnormal	1 (1)	0 (0)
Weight decreased	1 (1)	0 (0)
Bone density decreased	1 (1)	0 (0)
Blood and lymphatic system disorders		
Splenomegaly	3 (3)	0 (0)
Thrombocytopenia	1 (1)	0 (0)
Cardiac disorders		
Palpitations	2 (2)	0 (0)
Atrioventricular block first degree	1 (1)	0 (0)
Atrioventricular block second degree	1 (1)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Neoplasm skin	1 (1)	0 (0)
Skin papilloma	1 (1)	0 (0)
Respiratory, thoracic and mediastinal disorders		
Throat irritation	2 (2)	0 (0)
Cough	1 (1)	0 (0)
Hepatobiliary disorders		
Cholelithiasis	1 (1)	0 (0)
Hepatomegaly	1 (1)	0 (0)
Psychiatric disorders		
Confusional state	1 (1)	0 (0)
Reproductive system and breast disorders		
Menstruation irregular	1 (1)	0 (0)
Polycystic ovaries	1 (1)	0 (0)
Ear and labyrinth disorders		
Tinnitus	1 (1)	0 (0)
Injury, poisoning and procedural complications		
Foreign body	1 (1)	0 (0)
Renal and urinary disorders		
Proteinuria	1 (1)	0 (0)
Vascular disorders		
Flushing	1 (1)	0 (0)

In a Phase 2 open-label, uncontrolled study (GZGD00304) with up to 4 years of treatment in 26 patients, the types and incidences of adverse reactions were similar to the ENGAGE and ENCORE studies.

Following completion of the extension periods from the uncontrolled Phase 2 study and Phase 3 clinical program, adverse reactions assessed as related to treatment were pooled from the primary analysis and uncontrolled extension periods of Trial 1 (ENGAGE), Trial 2 (ENCORE), the Phase 2 Study, and one supporting Phase 3b study, representing a total of 1400 patient-years of treatment exposure in 393 adult patients who received CERDELGA for a median treatment duration of 3.5 years (5 patients received CERDELGA for 9.3 years). The most commonly reported adverse reactions with CERDELGA (occurring in ≥ 5% of patients) were: dyspepsia (6%), headache (5%), abdominal pain upper (5%) and dizziness (5%). The most commonly reported serious adverse reaction was syncope (1%).

8.5 Post-Market Adverse Reactions

Respiratory, thoracic and mediastinal disorders:

Cough

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

In vitro, eliglustat is metabolized primarily by CYP2D6 and to a lesser extent by CYP3A. Eliglustat is also a substrate of P-glycoprotein (P-gp).

Drugs that inhibit CYP2D6 and CYP3A pathways may significantly increase the exposure and maximal concentration of eliglustat and result in prolongation of the PR, QTc, and/or QRS cardiac interval which could result in cardiac arrhythmias.

Use of CERDELGA with strong CYP3A inducers substantially decreases the exposure to eliglustat, which may reduce the therapeutic effectiveness of CERDELGA; therefore concomitant administration is not recommended.

Co-administration of CERDELGA with drugs that are substrates for P-gp or CYP2D6 may result in increased concentrations of the concomitant drug.

Caution should be observed if CERDELGA is used concomitantly with drugs that prolong the PR, QRS, and/or QTc intervals, or affect electrolyte levels, as pharmacodynamic interactions may result.

9.3 Drug-Behavioural Interactions

No formal studies have been conducted on the effects of CERDELGA on the ability to drive and use machines

9.4 Drug-Drug Interactions

Effect of Other Drugs on the pharmacokinetics of CERDELGA

CYP2D6 and CYP3A Inhibitors

Some inhibitors of CYP2D6 and CYP3A are contraindicated with CERDELGA depending on the patient's CYP2D6 metabolizer status (see 2 CONTRAINDICATIONS). Some CYP2D6 and CYP3A inhibitors are not recommended for use with CERDELGA or may require dosing adjustment of CERDELGA, depending on the patient's CYP2D6 metabolizer status, to reduce the risk of potential significant adverse reactions (see 4 DOSAGE AND ADMINISTRATION). Physiologic based pharmacokinetic (PBPK) Modelling was used to predict changes in exposure and maximal concentrations in EMs with mild, hepatic impairment co-administered with CYP2D6 or CYP3A inhibitors in arriving at dosing recommendations in GD1 patients (see 2 CONTRAINDICATIONS, 4 DOSAGE AND ADMINISTRATION **Table 1**, **Table 2** and **Table 3** and 10 CLINICAL PHARMACOLOGY).

Co-administration with CYP2D6 Inhibitors

In EMs (N=30/33 subjects) in a clinical trial, the C_{max} and AUC_{0-12} of eliglustat following administration of CERDELGA with paroxetine (a strong CYP2D6 inhibitor) 30 mg once daily increased 7.0-fold and 8.4-fold, respectively. The C_{max} and AUC_{0-12} of eliglustat after co-administration of CERDELGA with paroxetine in CYP2D6 EMs were 110 ng/mL and 847 hr*ng/mL respectively.

Co-administration with CYP3A Inhibitors

In EMs (N=31/33 subjects) in a clinical trial, the C_{max} and AUC_{0-12} of eliglustat following co-administration of CERDELGA with ketoconazole (a strong CYP3A inhibitor) 400 mg once daily increased 4.0-fold and 4.4-fold, respectively. The C_{max} and AUC_{0-12} of eliglustat after co-administration of CERDELGA with ketoconazole in CYP2D6 EMs were 71.0 ng/mL and 501 hr*ng/mL, respectively.

PBPK modeling/population PK modeling (Pop-PK) was used to arrive at increased exposure and maximal concentration estimates for CYP2D6 inhibitors or CYP3A inhibitors taken concomitantly with CERDELGA. The exposure and maximal concentration estimates were then used in arriving at dosing recommendations for these populations (see 2 CONTRAINDICATIONS, 4 DOSAGE AND ADMINISTRATION **Table 1**, **Table 2** and **Table 3** and 10 CLINICAL PHARMACOLOGY, Pharmacokinetics**)**.

CYP3A Inducers

Co-administration with CYP3A inducers

Systemic exposures (C_{max} and AUC_{0-12}) of eliglustat decreased by approximately 89% in CYP2D6 EMs (N=12) following co-administration of supra-therapeutic doses of CERDELGA 127 mg twice daily with rifampin (a strong CYP3A inducer) 600 mg PO once daily. 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 CYP2D6 PMs (N=6). Use of CERDELGA with strong CYP3A inducers is not recommended in EMs, IMs, and PMs (see 4 DOSAGE AND ADMINISTRATION **Table 1**, **Table 2** and **Table 3** and 10 CLINICAL PHARMACOLOGY, Pharmacokinetics**)**.

Co-administration with P-gp inhibitors
The effect of P-gp inhibitors on the systemic exposure of eliglustat has not been studied clinically.

Effect of CERDELGA on the pharmacokinetics of other drugs
CERDELGA is an inhibitor of CYP2D6 and P-gp.

Following supra-therapeutic multiple doses of CERDELGA 127 mg twice daily, systemic exposure of metoprolol (50 mg, single dose, a CYP2D6 substrate) increased compared to metoprolol administration alone. Mean C_{max} and $AUC_{0-\infty}$ increased by 1.7- and 2.3-fold, respectively, in EMs and by 1.2- and 1.6-fold, respectively in IMs. The mean C_{max} and $AUC_{0-\infty}$ of metoprolol after co-administration with CERDELGA in IMs were 144 ng/mL and 1460 hr*ng/mL, respectively, and in EMs were 108 ng/mL and 719 hr*ng/mL, respectively.

Following supra-therapeutic multiple doses of CERDELGA 127 mg twice daily in EMs and IMs or 84 mg twice daily in PMs, systemic exposures to digoxin (0.25 mg, single dose, P-gp substrate, with narrow therapeutic index) increased compared to digoxin administration alone. Mean C_{max} and AUC_{last} increased by 1.7- and 1.5-fold, respectively. The C_{max} and AUC_{last} of digoxin after co-administration were 1.89 ng/mL and 16.9 hr*ng/mL in one IM subject, respectively, and mean values were 1.68 ng/mL and 13.3 hr*ng/mL in EMs, respectively.

Co-administration of CERDELGA with drugs that are substrates for P-gp or CYP2D6 may result in increased concentrations of the concomitant drug (see **Table 6** below)**.**

Table 6 - Established or Potential Drug-Drug Interactions with agents whose exposure may be increased by CERDELGA

Concomitant Drug Class: Drug Name	Ref	Effect	Clinical comment and alteration of dosing.
P-gp Substrates (e.g. digoxin, colchicine, dabigatran, phenytoin, pravastatin)	CT	CERDELGA may increase P-gp substrate drug exposure and maximum concentrations	Measure serum digoxin concentrations before initiating CERDELGA. Reduce digoxin dose by 30% and continue monitoring. Lower doses of other substances which are P-gp substrates may be required.
CYP2D6 Substrates such as certain antidepressants (tricyclic antidepressants, e.g. nortriptyline, amitriptyline, imipramine, and desipramine), phenothiazines (e.g., perphenazine, chlorpromazine), dextromethorphan and atomoxetine metoprolol	CT	CERDELGA may increase CYP2D6 substrate drug exposure and maximum concentrations	Lower doses of medicinal products that are CYP2D6 substrates may be required and titrate to clinical effect. Monitor therapeutic drug concentrations, as indicated.

CT = Clinical Trial; Ref = Reference

See 10 CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug Interaction Studies

Drug Interaction Studies
Drug Interaction Studies
Drug Interaction Studies

Pharmacodynamic Drug Interactions

Drugs that Prolong the PR Interval:

CERDELGA has the potential to increase the PR interval in a concentration-related manner (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular: Electrocardiogram (ECG) Changes and Potential for Cardiac Arrhythmias and 10CLINICAL PHARMACOLOGY, *Electrocardiographic evaluation*). Caution is recommended if CERDELGA is used concomitantly with other drugs that prolong the PR interval, including, but not limited to, certain antiarrhythmics, beta blockers, non-dihydropyridine calcium channel blockers, digitalis glycosides, sphingosine-1 phosphate receptor modulators, HIV protease inhibitors, somatostatin analogues, and glucagon-like peptide-1 analogues.

Drugs that Prolong the QRS and/or QTc Interval:

CERDELGA has the potential to increase the QRS duration and QTc interval in a concentration-related manner (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular: Electrocardiogram (ECG) Changes and Potential for Cardiac Arrhythmias and 10CLINICAL PHARMACOLOGY, *Electrocardiographic evaluation* . Concomitant use of CERDELGA with Class IA, IC, and III antiarrhythmics is not recommended. Caution should be observed if CERDELGA is used with other drugs that prolong the QTc and/or QRS intervals, including, but not limited to, the following: antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, risperidone, ziprasidone); antidepressants (e.g., fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants e.g., amitriptyline, imipramine, maprotiline); opioids (e.g., methadone); macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, telithromycin, tacrolimus); quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin); pentamidine; antimalarials (e.g., quinine, chloroquine); azole antifungals (e.g., ketoconazole, fluconazole, voriconazole); domperidone; 5-hydroxytryptamine (5-HT)3 receptor antagonists (e.g., ondansetron); tyrosine kinase inhibitors (e.g., sunitinib, nilotinib, vandetanib); histone deacetylase inhibitors (e.g., vorinostat); beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol).

The above lists of potentially interacting drugs are not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QTc interval, the QRS duration, or the PR interval, as well as for older drugs for which these effects have recently been established.

Drugs that Affect Electrolytes**:**
Caution is recommended if CERDELGA is used with drugs that have the potential to decrease electrolytes levels, including, but not limited to, loop, thiazide, and related diuretics, laxatives and enemas, amphotericin B, high dose corticosteroids, and proton pump inhibitors. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular

The above list of potentially interacting drugs is not comprehensive. Current information sources should be consulted for newly approved drugs that disrupt electrolytes, as well as for older drugs for which these effects have recently been established.

9.5 Drug-Food Interactions

Grapefruit products contain one or more components that strongly inhibit CYP3A and can increase plasma concentrations of eliglustat. Consumption of grapefruit or its juice should be avoided while taking CERDELGA (see **Table 1**, **Table 2** and **Table 3** in 4 DOSAGE AND ADMINISTRATION).

9.6 Drug-Herb Interactions

Use of a strong CYP3A inducer (e.g. St. John's wort) with CERDELGA is not recommended in IMs, EMs and PMs. The use of weak CYP3A inhibitors (e.g. goldenseal) is not recommended in PMs (see **Table 1**, **Table 2** and **Table 3** in 4 DOSAGE AND ADMINISTRATION).

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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". Eliglustat is a specific inhibitor of glucosylceramide synthase (IC50 = 10 ng/mL), and acts as a substrate reduction therapy for GD1.

10.2 Pharmacodynamics

Electrocardiographic evaluation
In a randomised, double-blind, placebo- and positive-controlled, crossover ECG assessment study, healthy subjects (N=47) received single 168 mg and 672 mg doses of CERDELGA, producing mean C_{max} values of 16.7 ng/mL and 237 ng/mL, respectively, with upper range concentrations as high as 761 ng/mL. Of note, mean steady-state C_{max} values for eliglustat in patients with Gaucher disease receiving the recommended therapeutic doses are predicted to be approximately 25 ng/mL in extensive metabolisers and approximately 75 ng/mL in intermediate and poor metabolisers on the basis of a population pharmacokinetic model.

At the CERDELGA 168 mg single dose, there were statistically significant differences from placebo in baseline-adjusted mean QRS duration and PR interval, with maximum effects of 1.4 ms (90% CI 0.4, 2.3) for the QRS duration and 3.5 ms (90% CI 1.2, 5.8) for the PR interval. At the CERDELGA 672 mg single dose, there were statistically significant differences from placebo in baseline-adjusted mean QTc interval, QRS duration, and PR interval, with maximum effects of 6.5 ms (90% CI 3.6, 9.3) for the QTcF interval, 4.2 ms (90% CI 3.1, 5.2) for the QRS duration, and 14.1 ms (90% CI 11.7, 16.6) for the PR interval.

Concentration-related increases were observed for the placebo corrected change from baseline in the PR, QRS, and QTc intervals. Based on a PK/PD model, from this single dose study in healthy subjects, the magnitude of ECG interval changes at ascending plasma concentrations is predicted to be as follows (**Table 7**):

Table 7 - PK/PD Model-Predicted Values of Placebo-Corrected Change from Baseline in ECG Parameters at Mean Maximal Plasma Concentrations (C_{max})

PBPK/Population PK Model-Predicted Mean C_{max} of Eliglustat (ng/mL) (CYP2D6 Phenotypes, Dose)	PR interval (ms) Mean (90% CI)	QTcF Interval (ms) Mean (90% CI)	QRS Duration (ms) Mean (90% CI)
25 (CYP2D6 EM, CERDELGA 84 mg BID)	1.6 (0.5, 2.8)	0.4 (-1.0, 1.7)	0.4 (-0.3, 1.1)
75.2 (CYP2D6 PM, CERDELGA 84 mg QD)	3.4 (2.3, 4.6)	1.6 (0.3, 3.0)	1.0 (0.3, 1.7)
75.6 (CYP2D6 IM, CERDELGA 84 mg BID)	3.5 (2.3, 4.6)	1.7 (0.3, 3.0)	1.0 (0.3, 1.7)
87.4 (CYP2D6 EM, CERDELGA 84 mg BID + strong CYP3A inhibitor)	3.9 (2.7, 5.1)	2.0 (0.6, 3.3)	1.1 (0.4, 1.8)
163 (CYP2D6 IM, CERDELGA 84 mg BID + strong CYP2D6 inhibitor)	6.6 (5.4, 7.8)	3.9 (2.5, 5.2)	2.1 (1.4, 2.8)
321 (CYP2D6 PM, CERDELGA 84 mg QD + strong CYP3A inhibitor)	12.3 (11.0, 13.6)	7.8 (6.3, 9.4)	4.0 (3.3, 4.8)
337 (CYP2D6 IM, CERDELGA 84 mg BID + strong CYP3A inhibitor)	12.9 (11.5, 14.2)	8.2 (6.7, 9.8)	4.2 (3.5, 5.0)
507 (CYP2D6 EM, CERDELGA 84 mg BID + strong CYP3A inhibitor + strong CYP2D6 inhibitor)	19.0 (17.4, 20.6)	12.5 (10.6, 14.4)	6.3 (5.5, 7.1)
578 (CYP2D6 IM, CERDELGA 84 mg BID + strong CYP3A inhibitor + strong CYP2D6 inhibitor)	21.6 (19.8, 23.3)	14.3 (12.3, 16.4)	7.2 (6.3, 8.1)

BID = twice daily; C_{max} = maximum observed plasma concentration; IM = intermediate metabolizer; EM = extensive metabolizer; QD = once daily; PM = poor metabolizer.

In the consideration of multiple dose data, the results of a multiple ascending-dose, randomised, double-blind, placebo-controlled study in healthy subjects are also presented. The study included cohorts of 12 subjects (N=8 active, N=4 placebo) who received CERDELGA at doses of 42 mg BID, 168 mg BID, or 294 mg BID or placebo for 12 days. During serial ECG assessments on day 12 of treatment, the observed maximum placebo-adjusted mean change from baseline in the QTcF interval was 9.6 ms (90% CI 5.3, 13.9) in the 42 mg BID cohort and 16.1 ms (90% CI 4.4, 27.9) in the 168 mg BID cohort, while the maximum placebo-adjusted mean change from baseline in the PR interval was 7.3 ms (90% 1.0, 13.5) in the 42 mg BID cohort and 8.3 ms (90% CI 2.3, 14.3) in the 168 mg BID cohort and the maximum placebo-adjusted mean change from baseline in the QRS duration was 5.4 ms (90% CI 4.4, 6.3) in the 42 mg BID group and 3.6 ms (1.0, 6.1) in the 168 mg BID group. A high discontinuation rate in the 294 mg BID group precluded informative ECG data for this dose (between 2 and 5 subjects on day 12).

ECG data from this study should be interpreted with the understanding that there was a small number of subjects analyzed at each dose in addition to high pharmacokinetic variability at each dose level (see

7 WARNINGS AND PRECAUTIONS, Cardiovascular and Monitoring and Laboratory Tests and 9DRUG INTERACTIONS, Pharmacodynamic Drug Interactions).

10.3 Pharmacokinetics

The systemic exposure (C_{max} and AUC) of eliglustat depends on the CYP2D6 phenotype. In healthy CYP2D6 EMs and IMs, CERDELGA pharmacokinetics is time-dependent and the systemic exposure increases in a more than dose proportional manner over the dose range of 42 to 127 mg twice daily. After multiple oral doses of 84 mg twice daily in EMs, steady state was reached in 4 days and eliglustat systemic exposure (AUC_{0-12}) increased up to about 2-fold (accumulation ratio) at steady state compared to after the first dose ($AUC_{0-\infty}$).

Oral 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. The pharmacokinetics of CERDELGA in CYP2D6 PMs is expected to be linear and time independent. Compared to EMs, the systemic exposure (AUC_{0-12}) following 84 mg twice daily at steady state is 7.7-fold higher in PMs in healthy subjects and 2.6-fold higher in IMs in healthy subjects. Both AUC_{0-12} and C_{max} for eliglustat in GD1 EM and IM patients were 1.4-fold and 1.3-fold higher compared to healthy EM and IM subjects.

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 were 19.5 ng/mL and 28.1 ng/mL in EM healthy subjects and EM GD1 patients respectively. Their respective mean AUC_{0-12} values were 119 hr*ng/mL and 168 hr*ng/mL in EM healthy subjects and EM GD1 patients respectively. The C_{max} and AUC0-12 in one IM healthy subject receiving multiple doses of CERDELGA 84 mg two time daily was 44.6 ng/mL and 306 hr*ng/mL, respectively. The mean C_{max} and AUC0-12 in four IM GD1 patients were 58.7 ng/mL and 400 hr*ng/mL, respectively. The oral bioavailability is low in EMs (<5%) following a 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 AUC0-12 values were 113 ng/mL and 922 hr*ng/mL, respectively.

Oral dosing of CERDELGA 84 mg once daily has not been studied in PMs. The predicted C_{max} and AUC0-24hr in PMs using 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 $AUC_{0-\infty}$. Food does not have a clinically relevant effect on CERDELGA 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 administration, the volume of distribution was 835 L in CYP2D6 EMs, suggesting wide distribution to tissues in humans.

Metabolism:
Eliglustat is extensively metabolized with high clearance, mainly by CYP2D6 and to a lesser extent CYP3A. 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 21 oxidative metabolites. No active metabolites have been identified that are expected to contribute to the pharmacological activity of CERDELGA.

Excretion:
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 intravenous administration in healthy volunteers, eliglustat total body clearance was 88 L/h in CYP2D6 EMs (CERDELGA is only for oral use). After repeated oral doses of 84 mg CERDELGA twice daily, eliglustat elimination half-life is approximately 6.5 hours in CYP2D6 EMs and 8.9 hours in PMs.

Table 8 - Mean (Standard deviation) [Minimum – Maximum] PK exposures after multiple dosing of CERDELGA to healthy subjects and GD1 patients

Population	Dose (mg, BID)	CYP2D6 Phenotype	C_{max} (ng/mL)	AUC_{0-12} (hr*ng/mL)
Healthy Subjects	84	EM (n=64)	19.5 (17.4) [2.67-68.4]	119[a] (113) [21.2-503]
	84	IM (n=1)	44.6	306
	84	PM (n=6)	113 (36.1) [70.8-172]	922 (304) [609-1476]
GD1 Patients	84	EM (n=60)	28.1 (19.4) [3.48-91.6]	168[b] (112) [30.6-662]
	84	IM (n=4)	58.7 (32.7) [40.4-108]	400 (286) [248-830]
	42	PM (n=5)	70.9 (37.4) [40.1-136]	583 (247) [323-992]

AUC_{0-12} = area under the plasma concentration versus time curve from time zero to the end of the dosing interval (12 hours); BID = twice daily; C_{max} = maximum observed plasma concentration; IM = intermediate metabolizer; EM = extensive metabolizer; PM = poor metabolizer
a. n=62
b. n=58

Drug Interaction Studies
Effect of other drugs on the Pharmacokinetics of CERDELGA
CYP2D6 and CYP3A inhibitors
Physiologic based pharmacokinetic modeling /Population PK modeling (PoP- PK) was used to arrive at increased exposure and maximal concentration estimates for CYP3A inhibitors or CYP2D6 inhibitors taken concomitantly with CERDELGA or strong/moderate CYP2D6 inhibitors used **concomitantly** with strong/moderate CYP3A inhibitors and CERDELGA. The exposure and maximal concentration estimates were then used in arriving at dosing recommendations for these populations (see 9 DRUG INTERACTIONS and **4** DOSAGE AND ADMINISTRATION).

Co-administration of CERDELGA with strong/moderate CYP2D6 inhibitors used concomitantly with strong/moderate CYP3A inhibitors is contraindicated in CYP2D6 EM and IM subjects. There were 4.2-17-fold increases for C_{max} and 5.0-24-fold increases for $AUC_{0-12,}$ after co-administration compared to CERDELGA administered alone in IM and EM subjects.

Co-administration of CERDELGA with strong CYP3A inhibitors is contraindicated in CYP2D6 IM and PM subjects. There were 4.3-4.4-fold increases for C_{max} (IM and PM), and 5.4 for AUC_{0-12} (IM) and 6.2 for AUC_{0-24} (PM), after co-administration, compared to CERDELGA administered alone.

Table 9 - Observed or predicted effect of CYP2D6 and/or CYP3A inhibitors for CERDELGA doses of 84 mg BID and QD in CYP2D6 Extensive Metabolizer (EM) and Intermediate Metabolizer (IM) populations

Concomitant Drug Class (Perpetrator)	Dose frequency (84 mg)	Ref	Extensive Metabolizers (EMs)			Intermediate Metabolizers (IMs)		
			C_{max} (ng/mL)	AUC_{0-12} (hr*ng/mL)	AUC_{0-24} (hr*ng/mL)	C_{max} (ng/mL)	AUC_{0-12} (hr*ng/mL)	AUC_{0-24} (hr*ng/mL)
Strong CYP2D6 Inhibitor + Strong CYP3A Inhibitor (paroxetine + ketoconazole)	BID	P	507	6163	-	578	7106	-
Moderate CYP2D6 Inhibitor + Moderate CYP3A Inhibitor (terbinafine + fluconazole)	BID	P	309	3488	-	321	3615	-
Strong CYP2D6 Inhibitor (paroxetine)	BID	CT/P	135	1168	-	163	1677	-
Moderate CYP2D6 Inhibitor (terbinafine)	BID	P	115	1149	-	119	1190	-
	QD	P	84.4	-	1126	86.7	-	1182
Weak CYP2D6 Inhibitor (ritonavir)	BID	P	42.1	361	-	81.3	753	-
Strong CYP3A Inhibitor (ketoconazole)	BID	CT/P	87.4	691	-	337	3917	-
	QD	P	46.9	-	576	181	-	3120
Moderate CYP3A Inhibitor (fluconazole)	BID	P	84.2	823	-	195	2062	-
	QD	P	38.7	-	434	108	-	1539
Weak CYP3A Inhibitor (fluvoxamine)	BID	P	48.4	415	-	105	976	-

AUC_{0-12} = area under the plasma concentration versus time curve from time zero to the end of the dosing interval (12 hours for BID); AUC_{0-24} = area under the plasma concentration versus time curve from time zero to the end of the dosing interval (24 hours for QD); BID = Twice daily; C_{max} = maximum observed plasma concentration; CT = Clinical Trial; P = Physiologically-based pharmacokinetic prediction; QD = Once daily; Ref = Reference.
Scaling factors of 1.23 for C_{max} and 1.38 for AUC_{0-12} obtained from population PK analysis were applied to the clinical trial results and PBPK predicted values for GD1 patients

Table 10 - Predicted effect of CYP3A and/or CYP2D6 inhibitors for CERDELGA doses of 84 mg QD in CYP2D6 Poor Metabolizer (PM) populations

Concomitant Drug Class (Perpetrator)	Dose frequency (100 mg)	Ref	Poor Metabolizers (PMs)	
			C_{max} (ng/mL)	AUC_{0-24} (ng.h/mL)
Strong CYP2D6 Inhibitor + Strong CYP3A Inhibitor (paroxetine + ketoconazole)	QD	P	N/A[a]	N/A[a]
Moderate CYP2D6 Inhibitor + Moderate CYP3A Inhibitor (terbinafine + fluconazole)	QD	P	N/A[a]	N/A[a]
Strong CYP2D6 Inhibitor (paroxetine)	QD	P	N/A[b]	N/A[b]
Moderate CYP2D6 Inhibitor (terbinafine)	QD	P	N/A[b]	N/A[b]
Weak CYP2D6 inhibitor (ritonavir)	QD	P	N/A[b]	N/A[b]
Strong CYP3A Inhibitor (ketoconazole)	QD	P	321	5950
Moderate CYP3A Inhibitor (fluconazole)	QD	P	179	2820
Weak CYP3A Inhibitor (fluvoxamine)	QD	P	102	1290

AUC_{0-24} = area under the plasma concentration versus time curve from time zero to the end of the dosing interval (24 hours for QD); QD = Once daily; C_{max} = maximum observed plasma concentration; P = Physiologically-based pharmacokinetic prediction; Ref = Reference; N/A = Data not available

Scaling factors of 1.23 for C_{max} and 1.38 for AUC_{0-12} obtained from population PK analysis were applied to the PBPK predicted values for GD1 patients; a= Similar to or greater than that expected in the interaction with a strong/moderate CYP3A inhibitor alone as no drug interaction is expected with any CYP2D6 inhibitor due to little to no CYP2D6 activity in CYP2D6 PMs; b= No drug interaction is expected with any CYP2D6 inhibitor due to little to no CYP2D6 activity in CYP2D6 PMs.

Mild hepatic impaired patients co-administered with CYP2D6 and CYP3A inhibitors

Physiologic based pharmacokinetic modeling /Population PK modeling (Pop- PK) was used to arrive at increased exposure and maximal concentration estimates for CYP2D6 inhibitors or CYP3A inhibitors taken concomitantly with CERDELGA in EM patients with mild or moderate hepatic impairment.

Co-administration of CERDELGA with strong or moderate CYP2D6 inhibitors is contraindicated in CYP2D6 EM patients with mild hepatic impairment. There were approximately 2- 4 fold increases for C_{max} and approximately 2-5 fold increases for AUC_{0-12} after co-administration, compared to CERDELGA administered alone in EM patients with mild hepatic impairment.

Co-administration of CERDELGA with strong CYP3A inhibitors is contraindicated in CYP2D6 EM patients with mild hepatic impairment. There were approximately 3-fold increases for C_{max} and approximately

4-fold increases for AUC_{0-12} after co-administration, compared to CERDELGA administered alone in EM patients with mild hepatic impairment.

Table 11 - Observed or Predicted effect of CYP2D6 and/or CYP3A inhibitors for CERDELGA doses of 84 mg BID and QD in CYP2D6 Extensive Metabolizer (EM) hepatic impaired GD1 patient populations

Hepatic Impairment status +inhibitor	Dosing frequency (84 mg)	Ref	C_{max} (ng/mL)	AUC_{0-12} (ng*h/mL)	AUC_{0-24} (ng*h/mL)
Mild hepatic impairment	Single Dose	CT[a]	22.4	-	172[b]
	BID	P	79.0	784	-
	QD	P	40.5	-	484
Moderate hepatic impairment	Single Dose	CT[a]	39.5	-	575[b]
	BID	P	213	2434	-
	QD	P	103	-	1757
Mild hepatic impairment + strong CYP2D6 inhibitor (paroxetine)	BID	P	310	3621	-
Mild hepatic impairment + moderate CYP2D6 inhibitor (terbinafine)	BID	P	182	1972	-
Mild hepatic impairment + weak CYP2D6 inhibitor (ritonavir)	BID	P	107	1100	-
	QD	P	56.0	-	730
Mild hepatic impairment + strong CYP3A inhibitor (ketoconazole)	BID	P	253	3028	-
Mild hepatic impairment + moderate CYP3A inhibitor (fluconazole)	BID	P	178	2013	-
	QD	P	65.8	-	966
Mild hepatic impairment + weak CYP3A inhibitor (fluvoxamine)	BID	P	110	1132	-
	QD	P	52.2	-	665

AUC_{0-12} = area under the plasma concentration versus time curve from time zero to the end of the dosing interval (12 hours for BID); AUC_{0-24} = area under the plasma concentration versus time curve from time zero to the end of the dosing interval (24 hours for QD); BID = Twice daily; C_{max} = maximum observed plasma concentration; CT = Clinical Trial; P = Physiologically-based pharmacokinetic prediction; QD = Once daily; Ref = Reference.

Scaling factors of 1.23 for C_{max} and 1.38 for AUC_{0-12} obtained from population PK analysis were applied to PBPK predicted values for GD1 patients

a. Clinical trial data in hepatic impaired patients administered single dose of eliglustat 84 mg.

b. Value represents AUC (area under the plasma concentration versus time curve from time zero to infinity) after single dose

Effect of OATP (organic anion transporting polypeptide) Inhibitors on CERDELGA PK

Systemic exposures of eliglustat were similar with or without co-administration of CERDELGA and a single 600 mg IV dose of rifampin (a potent OATP inhibitor), regardless of CYP2D6 phenotypes. The C_{max} and AUC_{last} after co-administration were 60.5 ng/mL and 611 hr*ng/mL for CYP2D6 PMs (CERDELGA 84 mg with rifampin 600 mg), and were 22.6 ng/mL and 186 hr*ng/mL for CYP2D6 EM/IMs (CERDELGA 127 mg with rifampin 600 mg) respectively.

Effect of Gastric pH-Modifying Agents on CERDELGA PK

Gastric pH-modifying agents (Maalox®, Tums®, Protonix®) did not have a clinically relevant effect on CERDELGA exposure.

Co-administration of Maalox®, Tums®, Protonix® with a single 84 mg dose of CERDELGA resulted in a 1.08-1.15-fold increase in C_{max} and 1.06-1.14-fold increase in AUC_{last} respectively compared to CERDELGA administered alone. After co-administration, the eliglustat C_{max} ranged from 8.10 to 9.06 ng/mL and AUC_{last} ranged from 61.8 to 68.7 hr*ng/mL, respectively.

Effect of CERDELGA on the pharmacokinetics of other drugs

CERDELGA 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 (see 9 DRUG INTERACTIONS).

In vitro, CERDELGA is a weak inhibitor of CYP3A. Repeated doses of CERDELGA 84 mg twice daily in CYP2D6 EM and PM population did not change the exposures to norethindrone (1.0 mg) and ethinyl estradiol (0.035 mg). The C_{max} and AUC_{last} after co-administration were 22.4 ng/mL and 147 hr*ng/mL for norethindrone, and 138 pg/mL and 1160 hr*pg/mL for ethinyl estradiol respectively.Therefore, CERDELGA is not expected to impact the efficacy or safety of oral contraceptives containing norethindrone and ethinyl estradiol.

Special Populations and Conditions

- **Pediatrics**

  Safety and effectiveness in pediatric patients have not been established.

- **Geriatrics**

  Clinical studies of CERDELGA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects (see 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

- **Sex**

  Based on the population pharmacokinetic analysis, body weight, gender and race had limited or no impact on the pharmacokinetics of CERDELGA.

- **Genetic Polymorphism**

  CYP2D6 phenotype

  Population pharmacokinetic analysis shows that the CYP2D6 predicted phenotype based on

genotype is the most important factor affecting pharmacokinetic variability. Individuals with a CYP2D6 PM predicted phenotype (approximately 5 to 10% of the population) exhibit higher eliglustat concentrations than CYP2D6 IMs or EMs.

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 8 ADVERSE REACTIONS and 14 CLINICAL TRIALS).

CERDELGA should not be used in patients who are CYP2D6 URMs or indeterminate metabolizers (see 1 INDICATIONS).

- **Hepatic Insufficiency**

  Effects of mild and moderate hepatic impairment were evaluated in a single dose phase 1 study. After a single 84 mg dose, eliglustat C_{max} AUC were 1.22 and 1.15-fold higher in CYP2D6 EMs with mild hepatic impairment, and 2.81- and 5.16-fold higher in CYP2D6 EMs with moderate hepatic impairment compared to healthy CYP2D6 EMs. After repeated 84 mg twice daily doses of CERDELGA, C_{max} and AUC0-12 are predicted to be 2.38- and 2.85 fold higher in CYP2D6 EMs with mild hepatic impairment and 6.41-and 8.86-fold higher in CYP2D6 EMs with moderate hepatic impairment compared to healthy EMs.

  Steady state PK exposure could not be predicted in CYP2D6 IMs and PMs with mild and moderate hepatic impairment due to limited or no single-dose data. The effect of severe hepatic impairment was not studied in subjects with any CYP2D6 phenotype (see 7 WARNINGS AND PRECAUTIONS, 2 CONTRAINDICATIONS and 4 DOSAGE AND ADMINISTRATION).

  Dosing adjustment is required in EMs with mild hepatic impairment. Contraindication or dose adjustment is required when CERDELGA is co-administered with CYP2D6 or CYP3A inhibitors, depending on the strength of the CYP2D6 or CYP3A inhibitor co-administered (see 4 DOSAGE AND ADMINISTRATION, 2 CONTRAINDICATIONS, 9 DRUG INTERACTIONS and 10 CLINICAL PHARMACOLOGY)

- **Renal Insufficiency**

  The effect of severe renal impairment was evaluated in a single dose phase 1 study. After a single 84 mg dose, eliglustat C_{max}¬ and AUC decreased by 12% and 1% respectively, for CYP2D6 EMs with severe renal impairment and are comparable to the pharmacokinetic data of healthy CYP2D6 EMs. Limited or no data are available in patients with end stage renal disease (ESRD) and in CYP2D6 IMs or PMs with severe renal impairment (see 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

11 STORAGE, STABILITY AND DISPOSAL

Store at 20°C to 25°C with excursions permitted between 15°C and 30°C.

No protection from light and moisture is required.

12 SPECIAL HANDLING INSTRUCTIONS

No special handling instructions required.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

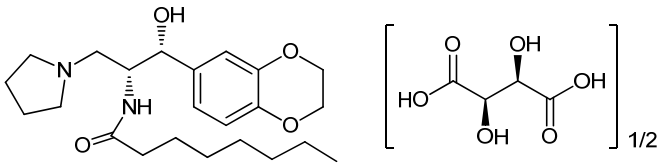
Drug Substance

Proper name: Eliglustat tartrate

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

Molecular formula and molecular mass: $C_{23}H_{36}N_2O_4$+½($C_4H_6O_6$) & 479.59

Structural formula:



Physicochemical properties: White to off-white crystalline powder that is highly soluble in water.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Indication: Gaucher disease type 1

Table 12 - Summary of Patient Demographics for Clinical Trials in Specific Indication

Study Name	Trial design	Dosage, route of administration and duration	Study subjects enrolled (n=number)	Median Age (range)	Gender
ENGAGE	Phase 3; Randomized, placebo- controlled Treatment-naïve GD1 patients	CERDELGA, capsule (oral); 42 mg or 84 mg BID Placebo 39 weeks	40 (20 on CERDELGA and 20 on placebo) CERDELGA Treatment Group: IM (5%), EM (90%), URM (5%) patients	30 (16-63)	Male (50%) and female (50%)
ENCORE	Phase 3; Randomized, open-label, active comparator Previously treated GD1 (stabilized with ERT)	CERDELGA Capsule (oral); 42 mg, 84 mg, or 127 mg BID Cerezyme®, IV – variable doses based on patients' previous dose history 52 weeks	159 (106 on CERDELGA and 53 on CEREZYME) CERDELGA Treatment Group: PM (4%), IM (10%), EM (80%), URM (4%) patients	37 (18-69)	Male (44%) and female (56%)
GZGD00304 (Phase 2)	Phase 2; Open-label Treatment-naïve GD1 patients	CERDELGA Capsule (oral); 42 mg or 84 mg BID 48 months	26 CERDELGA Treatment Group: PM (4%), EM (96%) patients	31 (19-61)	Male (38%) and female (62%)

GD1=Gaucher Disease Type 1; ERT=Enzyme Replacement Therapy; BID=twice daily; IM=Intermediate Metaboliser; EM=Extensive Metaboliser; URM=Ultra Rapid Metaboliser; PM=Poor Metaboliser; IV= Intravenous

Study results

CERDELGA in Treatment-Naïve GD1 Patients – (ENGAGE Trial)

The ENGAGE Trial was a randomized, double-blind, placebo-controlled, multi-centre clinical study in 40 patients with GD1. Patients were randomized in a 1:1 ratio to receive CERDELGA or placebo for the duration of the 9-month double-blinded primary analysis period. Patients presented with splenomegaly, anemia and /or thrombocytopenia, and were stratified according to baseline spleen volume (≤20 or >20 multiples of normal [MN]). In the CERDELGA group, 3 (15%) patients received a dose of 42 mg CERDELGA twice daily during the 9-month primary analysis period and 17 (85%) patients received a dose escalation to 84 mg twice daily based on plasma trough concentration.

A summary of changes in organ volumes and hematological parameters in treatment-naïve patients from ENGAGE is shown in **Table 13**.

Table 13 - Comparison of Organ Volume and Haematology Results from Treatment-Naïve Patients: ENGAGE

	CERDELGA (N=20)	Placebo** (N=20)	Difference (CERDELGA – Placebo) [95% CI]	p value*
Spleen Volume, mean (SD)				
Baseline, MN	13.89 (5.93) [N=20]	12.50 (5.96) [N=20]		
9 Months, absolute change	-3.7 (2.38) [N=20]	0.4 (1.05) [N=20]	-4.1 [-5.3, -2.9]	Not tested
9 Months, % change (primary endpoint)	-27.58 (12.59) [N=20]	2.07 (8.78) [N=20]	-30.0 [-36.8, -23.2]	<0.0001
Hemoglobin, mean (SD)				
Baseline, g/dL	12.05 (1.19) [N=20]	12.75 (1.63) [N=20]		
9 Months, g/dL change (secondary endpoint)	0.73 (1.09) [N=20]	-0.58 (0.89) [N=20]	1.2 [0.6, 1.9]	0.0006
Liver volume (MN), mean (SD)				
Baseline, MN	1.44 (0.35) [N=20]	1.36 (0.28) [N=20]		
9 Months, absolute change	-0.1(0.11) [N=20]	0.0 (0.11) [N=20]	-0.1 [-0.2, 0.0]	Not tested
9 Months, % change (secondary endpoint)	-5.45 (6.89) [N=20]	1.70 (8.00) [N=20]	-6.6 [-11.4, -1.9]	0.0072
Platelets, mean (SD)				
Baseline, $x10^9$/L	75.05 (14.10) [N=20]	78.48 (22.61) [N=20]		
9 Months, absolute change	23.9 (22.60) [N=20]	-7.0 (15.39) [N=20]	31.3 [18.8, 43.8]	Not tested
9 Months, % change (secondary endpoint)	31.71 (31.80) [N=20]	-8.77 (19.19) [N=20]	41.1 [24.0, 58.2]	<0.0001

MN = **M**ultiples of normal; SD = standard deviation

***** Estimates and p-value are based on ANCOVA model that includes treatment group, baseline spleen severity group (≤20MN, >20MN) and baseline parameter value.

** All patients transitioned to CERDELGA treatment after Month 9

During the open-label long term period with CERDELGA (ENGAGE extension phase), the patients with complete data who continued to receive CERDELGA showed evidence of improvements throughout the extension phase. Results (change from baseline) after 18 months, 30 months and 4.5 years of exposure to CERDELGA are presented below:

Table 14 – ENGAGE Results at 18 months, 30 months and 4.5 years

Visit		Spleen Volume (MN) % Change From Baseline	Hemoglobin (g/dL) Change From Baseline	Liver Volume (MN) % Change From Baseline	Platelet Count (mm^3) % Change From Baseline
18 months	N	38	39	38	39
	Mean	-46.50%	1.1	-13.70%	58.50%
	SD	9.75%	1.03	10.65%	40.57%
30 months	N	32	35	32	35
	Mean	-54.20%	1.4	-18.50%	74.60%
	SD	9.51%	0.93	11.22%	49.57%
4.5 years	N	13	12	13	12
	Mean	-65.50%	1.4	-23.40%	86.80%
	SD	7.43%	1.31	10.59%	54.20%

Long-Term Clinical Outcomes in Treatment-Naïve GD1 patients – Phase 2 Study GZGD00304
Study GZGD00304 (Phase 2) was a single-arm, open-label, multi-centre study of CERDELGA in 26 patients. Nineteen patients completed 4 years of treatment, and sixteen patients had an efficacy endpoint assessment at 8 years of treatment. Improvements from baseline in organ volume (spleen and liver) and hematological parameters (platelet count and haemoglobin level) were sustained through the 8 year treatment period.

CERDELGA in GD1 Patients Switching From ERT–ENCORE Trial
The ENCORE Trial was a randomized, open-label, active-controlled, non-inferiority, multicenter clinical study evaluating the efficacy and safety of CERDELGA compared with CEREZYME® in 159 GD1 patients previously treated with enzyme replacement therapy who met pre-specified therapeutic goals.

Patients were randomized 2:1 to receive CERDELGA or CEREZYME® for the duration of the 12-month primary analysis period. Seventy-five percent of patients randomized to CERDELGA were previously treated with CEREZYME®; 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: 20% on 42 mg twice daily, 32% on 84 mg twice daily and 48% on 127 mg twice daily. The CERDELGA treatment group was comprised of PM (4%), IM (10%), EM (80%) and URM (4%) patients.

Note: The approved dosage of CERDELGA is 84 mg once daily (PMs) or twice daily (IMs or EMs) (see 4 DOSAGE AND ADMINISTRATION).

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 CEREZYME® 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 CEREZYME® 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 CEREZYME® 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 CEREZYME® patients remained within therapeutic goals for GD1.

Table 15 - Organ Volume and Hematology Results in Patients Switching from ERT in the ENCORE Trial

	CERDELGA (N=99)	**CEREZYME® (N=47)***
Spleen Volume, mean (SD)		
Baseline, MN	3.23 (1.37) [N=70]	2.63 (1.08) [N=39]
12 Months, absolute change	-0.16 (0.46) [N=70]	-0.10 (0.30) [N=39]
12 Months, % change (secondary endpoint)	-6.17 (14.14) [N=70]	-3.01 (10.50) [N=39]
Hemoglobin, mean (SD)		
Baseline, g/dL	13.59 (1.25) [N=98]	13.80 (1.22) [N=47]
12 Months, g/dL change (secondary endpoint)	-0.21 (0.71) [N=98]	0.04 (0.66) [N=47]
Platelets, mean (SD)		
Baseline, $x10^9$/L	206.75 (80.74) [N=98]	192.30 (57.34) [N=47]
12 Months, absolute change	9.53 (40.35) [N=98]	6.04 (23.73) [N=47]
12 Months, % change (secondary endpoint)	3.79 (18.85) [N=98]	2.93 (11.89) [N=47]
Liver volume, mean (SD)		
Baseline, MN	0.95 (0.19) [N=98]	0.91 (0.16) [N=47]
12 Months, absolute change	0.02 (0.09) [N=98]	0.03 (0.10) [N=47]
12 Months, % change (secondary endpoint)	1.78 (9.64) [N=98]	3.57 (10.24) [N=47]
Percentage of Patents who Remained Stable for 52 Weeks: Composite Primary Endpoint		
n/N (%)	83/99 (83.8)	44/47 (93.6)

ERT = enzyme replacement therapy; MN = multiples of normal; SD = standard deviation

***** All patients transitioned to CERDELGA treatment after Month 12

During the open-label long term treatment period with CERDELGA (ENCORE extension phase), 141 out of 146 patients (42 patients previously treated with enzyme replacement therapy and 99 who

continued treatment with CERDELGA) were evaluated for stability (composite of spleen and liver volumes, hemoglobin level and platelet count as defined in the first 12 months of the trial). The percentage of patients with complete data meeting the composite stability endpoint was 84.6% (n=115/136) after 2 years, 84.4% (n=92/109) after 3 years and 91.1% (n=41/45) after 4 years. The majority of patients with available data showed stability in individual disease parameters (spleen volume, liver volume, hemoglobin level and platelet count) through 4 years.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

The principal target organs for eliglustat in toxicology studies are the GI tract, lymphoid organs, liver (rat only) and reproductive system (male rat only). Effects of eliglustat in toxicology studies were reversible and exhibited no evidence of delayed or recurring toxicity. Safety margins for the chronic rat and dog studies ranged between 8-fold and 15-fold.

Eliglustat did not have significant effects on CNS or respiratory functions.

Carcinogenicity:

Carcinogenic potential of eliglustat 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.

Reproductive and Developmental Toxicology:

In a fertility and early embryonic development study in rats, eliglustat increased pre-implantation loss at 30 mg/kg/day (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).

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, 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. 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).

In separate studies, placental transfer and milk excretion of eliglustat and/or its metabolites were detected at trace amounts in the rat.

Mutagenesis:

Eliglustat was negative in the Ames test, chromosome aberration test in human peripheral blood lymphocytes, and in vivo oral mouse micronucleus test.

Safety Pharmacology:

Eliglustat resulted in a concentration-dependent suppression of hERG potassium currents and hNav1.5 sodium currents in HEK293 cells, with IC_{50} values of 0.35 µg/mL and 5.2 µg/mL, respectively, based on nominal concentrations.

Eliglustat resulted in a concentration-dependent suppression of hCav1.2 L-type calcium currents in Chinese hamster ovary cells, with an IC_{50} of 10.4 µg/mL based on nominal concentrations.

Conscious telemetered male dogs (N=4) were dosed with eliglustat by oral gavage according to an ascending dose regimen. Eliglustat at 1 to 80 mg/kg had no effect on arterial blood pressure or on QT, QTcF and QTcQ intervals. Eliglustat at 1 to 25 mg/kg had no effect on the PR interval. However, there was a tendency for prolongation of the PR interval with 50 and 80 mg/kg eliglustat, with maximum increases of 19.2 and 21 ms, respectively. Eliglustat at 1 and 3 mg/kg had no effect on QRS duration. However, a dose-dependent prolongation of the QRS duration versus vehicle was seen following administration of 10, 25, 50 and 80 mg/kg eliglustat, with maximum increases of 3.0, to 10.7 ms over this dose range.

Sodium pentobarbitone-anaesthetised dogs were dosed intravenously with escalating doses of 1, 2.5, and 5 mg/kg eliglustat (N=6) or vehicle (N=5) according to a parallel group design. At 2.5 mg/kg and 5 mg/kg eliglustat, dose-related increases were also seen in the PR interval (vehicle-adjusted mean change from baseline: 14.6 ± 8.7% and 24.7 ±9.8%, respectively), the QTcF interval (vehicle-adjusted mean change from baseline: 4.5 ± 2.9% and 6.9 ± 4.9%, respectively), and the QRS duration (vehicle-adjusted mean change from baseline: 4.3 ±4.6% and 13.3 ± 7.7%, respectively) at 5 min post-dose. Plasma levels of eliglustat at the end of each IV infusion were 2, 4.5, and 7.7 µg/mL for the 1, 2.5, and 5 mg/kg doses, respectively.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrCERDELGA™
Eliglustat Capsules

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

What is CERDELGA used for?

CERDELGA is used to treat adults, with Gaucher disease type 1, who:

- process CERDELGA at a regular speed (extensive metabolizers or EMs).
- process CERDELGA at a slower speed (intermediate metabolizers or IMs).
- process CERDELGA at a very slow speed (poor metabolizers or PMs).

Your healthcare professional will perform a test to make sure that CERDELGA is right for you. This test will tell your healthcare professional how quickly your body processes (metabolizes) CERDELGA. It will also determine if and how you can use this medicine.

How does CERDELGA work?

Gaucher disease type 1 is caused by not having the normal amount of an enzyme called acid β-glucosidase. This enzyme's job is to break down a lipid, or fatty substance, in your body called glucosylceramide. CERDELGA lowers the production of a lipid called glucosylceramide in the body. This helps the organs, like your liver and spleen, to work better.

Gaucher disease type 1 is a lifelong condition. You must continue to take CERDELGA as prescribed by your healthcare professional.

What are the ingredients in CERDELGA?

Medicinal ingredients: eliglustat (as eliglustat tartrate)

Non-medicinal ingredients: ammonium hydroxide, black iron oxide (E172), gelatin, glyceryl behenate/glycerol dibehenate, hypromellose, indigotine (E132), lactose monohydrate, microcrystalline cellulose, propylene glycol, shellac glaze, candurin silver fine, yellow iron oxide (E172) and potassium aluminum silicate (E555)

CERDELGA comes in the following dosage forms:

Capsules; 84 mg

Do not use CERDELGA if:

- you are allergic to eliglustat tartrate or any of the other ingredients of CERDELGA or the container
- you have one of the following rare genetic disorders, because lactose is a non-medicinal ingredient in CERDELGA:
  - Galactose intolerance
  - Lapp lactase deficiency

- Glucose-galactose malabsorption
- are an **extensive or intermediate metabolizer**, and
  - you are taking a combination of other medicines called **strong or moderate CYP2D6 inhibitors** with **strong or moderate CYP3A inhibitors**. The combination of these types of medicine will affect how you respond to CERDELGA.
- are an **intermediate or poor metabolizer**, and
  - you are taking medicines that are **strong CYP3A inhibitors**. Medicines of this type will affect how you respond to CERDELGA, or
  - you have liver problems.
- are an **extensive metabolizer** and you also have one of the following:
  - moderate to severe liver problems, or
  - mild liver problems and you are taking a **strong or moderate CYP2D6 inhibitor**, or
  - mild liver problems and you are taking a **strong CYP3A inhibitor**

Examples of **strong or moderate CYP2D6 inhibitors** are paroxetine, fluoxetine, quinidine, bupropion or terbinafine, duloxetine, moclobemide, mirabegron, cinacalcet and dronedarone.

Examples of **moderate CYP3A inhibitors** are cobicistat, indinavir, fluconazole, erythromycin, ciprofloxacin, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib and cimetidine.

Examples of **strong CYP3A inhibitors** are ketoconazole, clarithromycin, itraconazole, lopinavir, ritanovir, saquinavir, cobicistat, indinavir, telaprevir, tipranavir, posaconazole, voriconazole, conivaptan and boceprevir.

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

- Have heart problems like heart failure, heart disease, history of a heart attack.
- Have a family history of sudden cardiac death before age 50 years.
- Have a history of fainting.
- Have an irregular or abnormal heartbeat, including a heart condition called long QT syndrome.
- Have kidney or liver problems.
- Have an eating disorder.
- Have low blood levels of potassium, magnesium, or calcium.
- Are dehydrated or suffer from excessive vomiting, diarrhea or sweating.
- Are pregnant, think that you may be pregnant or are planning to become pregnant. You must talk to your healthcare professional about whether you can take CERDELGA while you are pregnant.
- Are breast-feeding or planning to breastfeed. It is not known if CERDELGA passes into your breast milk. You and your healthcare professional will decide if you should take CERDELGA or breastfeed. You should not do both.
- If you are 65 years old or older.

Check-ups and testing: You will have regular visits with your healthcare professional during your treatment. These visits might include the following to monitor your health:

- electrocardiogram (ECG) to monitor your heart rhythm health.
- blood tests

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

The following may interact with CERDELGA:

- Medicines used to treat fungal infections (such as ketoconazole, fluconazole, terbinafine, itraconazole, posaconazole, voriconazole, amphotericin B)
- Medicines used to treat bacterial infections (such as clarithromycin, erythromycin, ciprofloxacin, moxifloxacin, levofloxacin, telithromycin, tacrolimus)
- Medicines used to treat malaria (such as quinine, chloroquine)
- Medicines used to treat HIV infection and AIDS (such as cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, atazanavir, darunavir, fosamprenavir)
- Medicines used to treat Hepatitis C infection (boceprevir)
- Medicines used to treat tuberculosis (such as rifampin, isoniazid, rifabutin)
- Medicines used to treat seizures (such as carbamazepine, phenobarbital, phenytoin)
- Medicines used for heart conditions or high blood pressure (such as quinidine, dronedarone, diltiazem, verapamil, amlopidine, digoxin, metoprolol)
- Medicines used to treat depression or other mental health problems (such as paroxetine, fluoxetine, bupropion, duloxetine, moclobemide, fluvoxamine, perphenazine, chlorpromazine, pimozide, haloperidol, droperidol, risperidone, ziprasidone, citalopram, venlafaxine, nortriptyline, amitriptyline, imipramine, desipramine, maprotiline, atomoxetine)
- Medicines used to treat overactive bladder (such as mirabegron)
- Medicines used to prevent nausea and vomiting (such as ondansetron, aprepitant)
- Medicines used to treat cancer (such as imatinib, sunitinib, nilotinib, vandetanib, vorinostat)
- Medicines used to treat breathing problems like asthma (such as salmeterol, formoterol)
- Medicines used to treat low levels of sodium in the blood (such as conivaptan)
- Medicines used to treat problems with the parathyroid gland (such as cinacalcet)
- Medicines used to treat gout (such as colchicine)
- Medicines used to treat cough (such as dextromethorphan)
- Medicines used to prevent stroke (such as dabigatran)
- Medicines used to treat high cholesterol levels (such as pravastatin)
- Medicines used to treat pneumonia caused by fungus (such as pentamidine)
- Medicine used to treat ulcers (cimetidine, ranitidine)
- Medicine to treat heartburn and acid reflux (such as proton pump inhibitors)
- St. John's wort, an herbal medicine used to treat depression
- Goldenseal, an herbal medicine used to treat the common cold
- Laxatives and enemas
- High dose corticosteroids used to treat inflammation and reduce the activity of the immune system
- Opioids (such as methadone)
- Domperidone, often used to increase milk supply in women who are breastfeeding
- Diuretics or "water pills"
- Grapefruit. Do not eat grapefruit or drink grapefruit juice since it may increase the level of

CERDELGA in your blood.

If you take any medicines for the conditions listed above, your healthcare professional may need to prescribe a different medicine, change your dose of the other medicines, or change your dose of CERDELGA.

How to take CERDELGA:

- Always take CERDELGA exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- CERDELGA can be taken with or without food.
- Take CERDELGA at the same time each day.
- Swallow CERDELGA whole with water. Do not open, crush, dissolve, or chew the capsule. If you cannot swallow the capsule whole, tell your healthcare professional.

Usual dose:

Your healthcare professional will decide on the dose that is right for you. It may be either one or two CERDELGA capsules per day. This will be based on any other medicines you may be taking and blood tests to determine:

- the type of metabolizer you are (how quickly your body breaks down CERDELGA), and
- if you have kidney or liver problems.

Overdose:

Symptoms of taking too much CERDELGA may include dizziness with loss of balance, slow heart rate, nausea, vomiting and light-headedness.

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

Missed Dose:

If you miss a dose take the next capsule at the usual time. Do not take a double dose to make up for a forgotten dose.

What are possible side effects from using CERDELGA?

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

Side effects may include:

- tiredness, sleepiness or drowsiness, low energy
- headache
- dizziness
- fainting
- nausea, diarrhea, gas, indigestion, constipation, stomach pain
- dry mouth, trouble swallowing
- trembling movements

- pain in the bones, chest, arms, legs or back
- cough
- acne, skin marks
- oral fungal infection
- change in taste, smell, touch
- weight or bone loss
- confusion
- flushing
- ringing, buzzing, clicking or hissing in the ears
- irregular periods

CERDELGA can cause abnormal blood test results. Your healthcare professional will decide when these are necessary and will interpret the results. They will tell you if your test results are abnormal and if you need treatment.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Changes in the electrical activity of your heart (ECG changes): palpitations, irregular heartbeat, dizziness, fainting, light headedness, shortness of breath			√

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

Reporting Side Effects

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

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

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

Storage:

- Keep out of reach and sight of children.

- Store at 20°C to 25°C.
- Do not use this medicine after the expiry date which is stated on the carton, sleeve and blister after 'EXP'. The expiry date refers to the last day of that month.

If you want more information about CERDELGA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's websitewww.sanofi.ca, or by calling 1-800-265-7927.

This leaflet was prepared by sanofi-aventis Canada Inc.

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