AUSTRALIAN PRODUCT INFORMATION – CERDELGA (ELIGLUSTAT)

1 NAME OF THE MEDICINE

Cerdelga (eliglustat)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Cerdelga capsule contains 84 mg eliglustat (equivalent to 100 mg eliglustat tartrate).

For the full list of excipients, see Section 6.1- List of excipients.

Eliglustat is a synthetic small molecule and is a white to off-white powder. Eliglustat tartrate is highly soluble in water. It has a pKa of 8.79 and log P of 2.84.

3 PHARMACEUTICAL FORM

Cerdelga is formulated as a hard capsule for oral administration.

Cerdelga is available as pearl blue-green opaque cap and pearl white opaque body capsules with "GZ02" printed in black on the capsule. The size of the capsule is 'size 2' (dimensions 18.0 x 6.4 mm).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Cerdelga is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1).

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Before initiation of treatment with eliglustat, patients should be genotyped for CYP2D6 to determine the CYP2D6 metaboliser status.

Eliglustat can be taken with or without food. Avoid consumption of grapefruit or grapefruit juice with eliglustat because grapefruit is a strong CYP3A inhibitor.

The capsules should be swallowed whole, preferably with water, and should not be crushed, dissolved, or opened.

If a dose is missed, the prescribed dose should be taken at the next scheduled time; the next dose should not be doubled.

CYP2D6 Intermediate Metabolisers (IMs) and Extensive Metabolisers (EMs):

The recommended dose of Cerdelga in CYP2D6 IMs and EMs is 84 mg twice daily taken orally.

Important dosing information

Co-administration of eliglustat with other CYP2D6 or CYP3A inhibitors affects its systemic exposure (see section 4.5 – Interaction with other medicines) and the following doses are recommended:

Intermediate Metabolisers (IMs) or Extensive Metabolisers (EMs)		
Concomitant medications	**Recommended dose**	**Important information**
None	84 mg twice daily	
Concomitantly with a Strong / Moderate CYP2D6 inhibitor and a Strong / Moderate CYP3A inhibitor	Contra-indicated	Risk of significant elevations in plasma concentrations (See section 4.3 - Contraindications) Ensure Alert Card is made available to patients
Strong CYP2D6 inhibitors	84 mg once daily	Risk of elevations in plasma concentrations (See section 4.4 special warnings and precautions for use). Ensure Alert Card is made available to patients
Moderate CYP2D6 inhibitors	84 mg twice daily – use caution	Consider option of reducing dose to once daily based on risk of elevations in plasma concentrations (See section 4.4 special warnings and precautions for use). Ensure Alert Card is made available to patients
Strong / Moderate CYP3A inhibitors	84 mg twice daily – use caution	Consider option of reducing dose to once daily based on risk of elevations in plasma concentrations (See section 4.4 special warnings and precautions for use). Ensure Alert Card is made available to patients

CYP2D6 Poor Metabolisers (PMs):

The recommended dose in CYP2D6 PMs is 84 mg once daily taken orally.

Dosing of Cerdelga 84 mg once daily has not been studied in CYP2D6 PMs. Based on physiologically-based pharmacokinetic (PBPK) modelling, the systemic exposures in PMs with 84 mg once daily dosing are predicted to be within the range of those observed in non-PM patients. Appropriate adverse event monitoring is recommended.

Co-administration of eliglustat in CYP2D6 PMs concomitantly with strong CYP3A inhibitors is contraindicated (see section 4.3- Contraindications).

CYP2D6 Ultra-Rapid Metabolisers (URMs) and Indeterminate Metabolisers:

Patients who are CYP2D6 ultra-rapid metabolisers (URMs) may not achieve adequate concentrations of Cerdelga to achieve a therapeutic effect.

A specific dosage cannot be recommended for those patients whose CYP2D6 genotype cannot be determined (indeterminate metabolisers).

Therefore, eliglustat should not be used in patients who are CYP2D6 ultra-rapid (URM), or indeterminate metabolisers.

Prior treatment with enzyme replacement therapy

In clinical trials enzyme replacement treatment was allowed up to the day before the first dose of eliglustat.

For patients with stable disease who switch from enzyme replacement therapy to eliglustat, monitoring for disease progression (e.g. after 6 months with regular monitoring thereafter) should be performed for all disease domains to evaluate disease stability. Reinstitution of enzyme replacement therapy or an alternative treatment modality should be considered in individual patients who have a sub-optimal response.

Special populations

Hepatic Impairment

Cerdelga is contraindicated in CYP2D6 IMs or PMs with any degree of hepatic impairment and in CYP2D6 EMs with moderate (Child–Pugh Class B) or severe (Child–Pugh Class C) hepatic impairment.

In CYP2D6 EMs with mild hepatic impairment (Child–Pugh Class A), no dose adjustment is required and the recommended dose is 84 mg eliglustat twice daily (see section 'Pharmacokinetics').

Dosing recommendation in CYP2D6 EM with hepatic impairment			
Concomitant medication	**Mild hepatic impairment**	**Moderate hepatic impairment**	**Severe hepatic impairment**
No use of CYP2D6 or CYP3A inhibitors	84mg twice daily	Contraindicated	Contraindicated
Strong or moderate CYP2D6 inhibitors	Contraindicated	Contraindicated	Contraindicated
Weak CYP2D6 inhibitors	84 mg once daily	Contraindicated	Contraindicated
Any CYP3A inhibitors	84 mg once daily	Contraindicated	Contraindicated

Renal Impairment

In CYP2D6 EMs with end stage renal disease, Cerdelga is not recommended.

In CYP2D6 IMs or PMs with mild, moderate or severe renal impairment or end stage renal disease, Cerdelga is not recommended.

In CYP2D6 EMs with mild, moderate or severe renal impairment, no dosage adjustment is required and the recommended dose is 84 mg eliglustat twice daily.

See Section 5.2 – Pharmacokinetic properties-Special Populations

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

Cerdelga is contraindicated in patients who are:

- CYP2D6 intermediate metabolisers (IMs) or extensive metabolisers (EMs) taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor
- CYP2D6 poor metabolisers (PMs) who are taking a strong CYP3A inhibitor.

Use of Cerdelga under these conditions results in substantially elevated eliglustat plasma concentrations. For a list of strong and moderate CYP2D6 and CYP3A inhibitors, see section 4.5- Interactions with other medicines.

Limited or no data are available in CYP2D6 IMs or PMs with any degree of hepatic impairment; use of Cerdelga in these patients is contraindicated since metabolism is the predominant route of elimination.

Due to significantly increased eliglustat plasma concentrations, Cerdelga is contraindicated in CYP2D6 EMs with moderate or severe hepatic impairment and in CYP2D6 EMs with mild hepatic impairment taking a strong or moderate CYP2D6 inhibitor.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Before initiation of treatment with Cerdelga, patients should be genotyped for CYP2D6 to determine the CYP2D6 metaboliser status. Cerdelga 84 mg should not be used in patients who are ultra-rapid metabolisers (URMs), or indeterminate metabolisers.

Drug-drug interactions

Cerdelga is contraindicated in patients who are:

- CYP2D6 intermediate metabolisers (IMs) or extensive metabolisers (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.

- CYP2D6 poor metabolisers (PMs) taking a strong CYP3A inhibitor.

Under these conditions both major metabolic pathways for eliglustat metabolism are impaired, with predicted substantially elevated eliglustat plasma concentrations. Although no significant QTc increases were seen in a thorough QT/QTc study in healthy volunteers (see section 5.1- Pharmacodynamics, Electrocardiographic evaluation), based on PK/PD modelling, eliglustat plasma concentrations 11-fold above those expected at the indicated dose are predicted to cause mild increases in the PR, QRS, and QTc intervals of 20.4, 7.1, and 14.2 msec, respectively. For more information see section 4.5- Interactions with other medicines.

For use of Cerdelga with one strong or moderate inhibitor of CYP2D6 or CYP3A, see section 4.5 - Interactions with other medicines.

Use of Cerdelga with strong CYP3A inducers substantially decreases the exposure to eliglustat, which may reduce the therapeutic effectiveness of Cerdelga; therefore co-administration is not recommended (see section 4.5- Interactions with other medicines).

Patients with pre-existing cardiac conditions

Use of Cerdelga in patients with pre-existing cardiac conditions has not been studied during clinical trials. Because eliglustat is predicted to cause mild increases in ECG intervals at substantially elevated plasma concentrations, use of eliglustat should be avoided in patients with cardiac disease (congestive heart failure, recent acute myocardial infarction, bradycardia, heart block, ventricular arrhythmia and structural heart disease associated with arrhythmia), long QT syndrome, and in combination with Class IA (e.g. quinidine) and Class III (e.g. amiodarone, sotalol) antiarrhythmic medications.

Lactose

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Use in hepatic impairment

Concomitant use of Cerdelga with CYP2D6 or CYP3A inhibitors in CYP2D6 EMs with mild hepatic impairment can result in further elevation of eliglustat plasma concentrations, with the magnitude of the effect depending on the enzyme inhibited and the potency of the inhibitor. In CYP2D6 EMs with mild hepatic impairment taking a weak CYP2D6 inhibitor or a strong, moderate or weak CYP3A inhibitor, a dose of 84 mg eliglustat once daily should be considered (see ‘Dosage and Administration’ and ‘Pharmacokinetics’).

See section 4.2 (Dose and Method of Administration) and 5.2 (Pharmacokinetic properties- Special populations)

Use in renal impairment

See section 4.2 (Dose and Method of Administration) and 5.2 (Pharmacokinetic properties- Special populations)

Use in the elderly

A limited number of patients aged 65 and over were enrolled in clinical trials. No significant differences were found in the efficacy and safety profiles of older patients and younger patients.

Paediatric use

The safety and efficacy of eliglustat in children under the age of 18 years has not been established. No data are available.

Effects on laboratory tests

There is no data available on the effects of Cerdelga on laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Eliglustat is metabolised primarily by CYP2D6 and to a lesser extent by CYP3A4. Eliglustat is also a substrate of the P-glycoprotein (P-gp) efflux transporter. Eliglustat is an inhibitor of P-gp and CYP2D6 *in vitro*.

The list of substances in this section is not an inclusive list and the prescriber is advised to consult the PI of all other prescribed medicines for potential drug-drug interactions with eliglustat.

Agents that may increase eliglustat exposure

Cerdelga is contraindicated in patients who are:

- CYP2D6 intermediate metabolisers (IMs) or extensive metabolisers (EMs) taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor (see Table 1)
- CYP2D6 poor metabolisers (PMs) taking a strong CYP3A inhibitor.

Under these conditions both major metabolic pathways for eliglustat metabolism are impaired, with predicted substantially elevated eliglustat plasma concentrations (predicted increase of up to 17-fold for C_{max} and 25-fold for AUC_{0-12}).

Table 1 - Agents that may increase eliglustat exposure

CYP2D6 Inhibitors		CYP3A Inhibitors	
Strong	**Moderate**	**Strong**	**Moderate**
paroxetine	duloxetine	itraconazole	fluconazole
fluoxetine	terbinafine	posaconazole	ciprofloxacin
quinidine	mirabegron	voriconazole	erythromycin

CYP2D6 Inhibitors		CYP3A Inhibitors	
Strong	**Moderate**	**Strong**	**Moderate**
bupropion	moclobemide	clarithromycin	ciclosporin
	tipranavir / ritonavir	boceprevir	cimetidine
	dronedarone	cobicistat	diltiazem
	cinacalcet	elvitegravir	verapamil
		indinavir	dronedarone
		lopinavir	imatinib
		saquinavir	amprenavir
		tipranavir / ritonavir	atazanavir / ritonavir
		telaprevir	darunavir
		grapefruit juice	darunavir / ritonavir
		saquinavir	aprepitant (dose dependent)

CYP2D6 inhibitors

In intermediate (IMs) and extensive metabolisers (EMs):

After repeated 84 mg twice daily doses of eliglustat in non-PMs, concomitant administration with repeated 30 mg once daily doses of paroxetine, a strong inhibitor of CYP2D6, resulted in a 7- and 9-fold increase in eliglustat C_{max} and AUC_{0-12}, respectively.

A dose of eliglustat 84 mg once daily should be considered when a strong CYP2D6 inhibitor (e.g. paroxetine, fluoxetine, quinidine, bupropion) is used concomitantly in IMs and EMs.

At 84 mg twice daily dosing with eliglustat in non-PMs, it is predicted that concomitant use of moderate CYP2D6 inhibitors (e.g. duloxetine, terbinafine) would increase eliglustat exposure approximately 4-fold. Use caution with moderate CYP2D6 inhibitors in IMs and EMs.

In extensive metabolisers (EMs) with hepatic impairment:

Concomitant medication	Mild hepatic impairment	Moderate hepatic impairment	Severe hepatic impairment
No use of CYP2D6 inhibitors	84mg twice daily	Contraindicated	Contraindicated
Strong or moderate CYP2D6 inhibitors	Contraindicated	Contraindicated	Contraindicated
Weak CYP2D6 inhibitors	84 mg once daily	Contraindicated	Contraindicated

CYP3A inhibitors

In intermediate (IMs) and extensive metabolisers (EMs):

After repeated 84 mg twice daily doses of eliglustat in non-PMs, concomitant administration with repeated doses of ketoconazole, a strong inhibitor of CYP3A and P-gp, resulted in 4-fold increases in eliglustat C_{max} and AUC_{0-12}; similar effects would be expected for other strong inhibitors of CYP3A (e.g. clarithromycin, itraconazole). Caution should be used with strong CYP3A inhibitors in IMs and EMs.

At 84 mg twice daily dosing with eliglustat in non-PMs, it is predicted that moderate CYP3A inhibitors (e.g. erythromycin, fluconazole) would increase eliglustat exposure approximately 3-fold. Use caution with moderate CYP3A inhibitors in IMs and EMs.

In extensive metabolisers (EMs) with hepatic impairment:

Concomitant medication	Mild hepatic impairment	Moderate hepatic impairment	Severe hepatic impairment
No use of CYP3A inhibitors	84mg twice daily	Contraindicated	Contraindicated
Any CYP3A inhibitors	84 mg once daily	Contraindicated	Contraindicated

In poor metabolisers (PMs):

At 84 mg once daily dosing with eliglustat in PMs, it is predicted that concomitant use of strong CYP3A inhibitors (e.g. ketoconazole, clarithromycin, itraconazole) would increase the C_{max} and AUC_{0-24} of eliglustat 4- and 6-fold. The use of strong CYP3A inhibitors is contraindicated in PMs.

At 84 mg once daily dosing with eliglustat in PMs, it is predicted that concomitant use of moderate CYP3A inhibitors (e.g. erythromycin, fluconazole) would increase the C_{max} and AUC_{0-24} of eliglustat 2- and 3-fold, respectively. Use of moderate CYP3A inhibitors with eliglustat is not recommended in PMs.

Caution should be used with weak CYP3A inhibitors (e.g. amlodipine, cilostazol, fluvoxamine, goldenseal, isoniazid, ranitidine, ranolazine) in PMs.

CYP2D6 inhibitors used simultaneously with CYP3A inhibitors

In intermediate (IMs) and extensive metabolisers (EMs):

At 84 mg twice daily dosing with eliglustat in non-PMs, it is predicted that the concomitant use of strong or moderate CYP2D6 inhibitors and strong or moderate CYP3A inhibitors would increase C_{max} and AUC_{0-12} up to 17- and 25- fold, respectively. The use of a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor is contraindicated in IMs and EMs.

Grapefruit products contain one or more components that inhibit CYP3A and can increase plasma concentrations of eliglustat. Excessive consumption of grapefruit or its juice should be avoided.

Agents that may decrease eliglustat exposure

Table 2 - Agents that may decrease eliglustat exposure

Strong CYP3A Inducers (list not exhaustive)
rifampicin
carbamazepine
phenobarbital
phenytoin
St. John's wort
rifabutin

Strong CYP3A inducers

After repeated 127 mg twice daily doses of eliglustat in non-PMs, concomitant administration of repeated 600 mg daily doses of rifampicin (a strong inducer of CYP3A as well as the efflux transporter P-gp) resulted in an approximately 85% decrease in eliglustat exposure. After repeated 84 mg twice daily doses of eliglustat in PMs, concomitant administration of repeated 600 mg once daily doses of rifampicin resulted in an approximately 95% decrease in eliglustat exposure. Use of strong CYP3A inducer (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, rifabutin and St. John's wort) with Cerdelga is not recommended in IMs, EMs and PMs.

Agents whose exposure may be increased by eliglustat

Eliglustat is an inhibitor of P-gp and CYP2D6 *in vitro*.

Table 3 - Agents whose exposure may be increased by eliglustat

P-gp Substrates	CYP2D6 Substrates (list not exhaustive)
digoxin	metoprolol
colchicine	tricyclic antidepressants, e.g. nortriptyline, amitriptyline, imipramine, clomipramine, desipramine
dabigatran	dextromethorphan, atomoxetine
phenytoin, pravastatin	phenothiazines

P-gp Substrates

Concomitant administration with digoxin, a P-gp substrate, resulted in a 1.7- and 1.5-fold increase in digoxin C_{max} and AUC_{last}, respectively. Lower doses of P-gp substrate drugs (e.g. digoxin, colchicine, dabigatran etexilate, phenytoin, pravastatin) may be required.

CYP2D6 Substrates

Concomitant administration with metoprolol, a CYP2D6 substrate, resulted in a 1.5- and 2.1-fold increase in metoprolol C_{max} and AUC, respectively. Lower doses of CYP2D6 substrate drugs may be required. These include certain antidepressants (tricyclic antidepressants, e.g. nortriptyline, amitriptyline, imipramine, desipramine), phenothiazines, dextromethorphan, atomoxetine and Class 1C antiarrhythmics (e.g. propafenone, flecainide).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Fertility studies in rats revealed no evidence of impaired fertility due to eliglustat treatment.

In a reproductive toxicity study with mature male rats reversible inhibition of spermatogenesis together with effects on sperm motility and morphology were observed at a systemically toxic dose (200 mg/kg/day: equivalent to approx. 20 times the clinical exposure, based on AUC) as well as increased germ cell necrosis and seminal vesicle inflammation at 100 mg/kg/day (equivalent to 10 times the clinical exposure, based on AUC).

Use in pregnancy

Category B3.

There are no or limited amount of data from the use of eliglustat in pregnant women. Eliglustat showed no embryofoetal toxicity in rats or rabbits at oral doses corresponding to approximately 4 times the clinical exposure (based on AUC). However, higher maternotoxic doses in rats (>16-fold clinical exposure based on AUC) showed an increased incidence of delayed ossification and skeletal malformations in an embryofoetal development study and increased postimplantation loss, reduced pup numbers, and lower pup body weight in a rat pre/postnatal study. Because animal reproduction studies are not always predictive of human response, eliglustat should only be used during pregnancy if the benefit clearly outweighs the risk.

Use in lactation

It is unknown whether eliglustat or its metabolites are excreted in human milk. However, in rats, there was decreased body weight gain in dams and offspring following daily administration of eliglustat through weaning. Therefore, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from eliglustat therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Cerdelga has no or negligible influence on the ability to drive and use machines. Patients should take care when driving or operating machinery until they know how this medicine could affect them.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects.

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

Summary of the safety profile

The majority of adverse drug reactions seen in clinical trials are mild and transient. The most commonly reported adverse reaction with Cerdelga is dyspepsia, in approximately 6% of the patients. About 2% of patients receiving Cerdelga in clinical trials permanently discontinued treatment due to any adverse reaction.

The most frequently reported serious adverse reaction in clinical studies was syncope (0.8%). All events were associated with predisposing risk factors and appeared to be vasovagal in nature. None of these events led to discontinuation from the study.

For information on using Cerdelga in special patient populations see section 4.4- Special warnings and precautions for use.

Tabulated list of adverse reactions

The overall adverse reaction profile of eliglustat is based on 1400 patient-years of treatment exposure and pooled results from the primary analysis periods and extension periods of two pivotal Phase 3 studies (ENGAGE and ENCORE) and one 8-year Phase 2 study (Study 304), and one supporting Phase 3b study (EDGE). In these four studies, a total of 393 patients between the ages of 16 – 75 years received eliglustat for a median treatment duration of 3.5 years (up to 9.3 years) and between the ages of 16 - 69 years.

The most common adverse drug reactions are presented in Table 4 using the following categories of frequency: common (≥1/100 to <1/10). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4 - Adverse Reactions occurring with eliglustat in >2% of the patients in the pivotal studies (ENGAGE and ENCORE), the Phase 2 Study 304 and the supporting Phase 3b study (EDGE)

System Organ Class	Common
Nervous system disorders	Headache*, dizziness*
Cardiac disorders	Palpitations
Gastrointestinal disorders	Dyspepsia, abdominal pain upper*, diarrhoea*, nausea, constipation, abdominal pain*, gastrooesophageal reflux disease, abdominal distension*, gastritis,
Musculoskeletal and connective tissue disorders	Arthralgia
General disorders and administration site conditions	Fatigue

* The incidence of the adverse reaction was the same or higher with placebo than with Cerdelga in the placebo-controlled pivotal study ENGAGE.

Post marketing

The following additional adverse reaction has been reported during post-approval use of Cerdelga. The adverse reaction is derived from spontaneous reports and therefore, the frequency is "not known" (cannot be estimated from the available data).

Respiratory, thoracic and mediastinal disorders:

Cough

4.9 OVERDOSE

The highest eliglustat plasma concentration experienced to date occurred in a Phase 1 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.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other alimentary tract and metabolism products, Various alimentary tract and metabolism products, ATC code: A16AX10.

Mechanism of action

Gaucher disease is caused by a deficiency of the lysosomal enzyme, acid β-glucosidase, which results in the accumulation of its major natural substrate, glucosylceramide (GL-1), especially in the liver, spleen, and bone marrow. Eliglustat is a potent and specific inhibitor of glucosylceramide synthase, and acts as a substrate reduction therapy for Gaucher disease type 1 (GD1). The goal of this approach is to reduce the rate of synthesis of glucosylceramide to match its impaired rate of catabolism in patients with GD1, thereby preventing glucosylceramide accumulation and alleviating clinical manifestations.

In clinical trials in treatment-naïve GD1 patients, plasma GL-1 levels were elevated in the majority of these patients and decreased with eliglustat treatment. Additionally, in a clinical trial in GD1 patients stabilised on enzyme replacement therapy (ERT) (i.e. having already achieved therapeutic goals on ERT prior to initiating eliglustat treatment), plasma GL-1 levels were normal in most patients and decreased with eliglustat treatment.

Cardiac Effects

Eliglustat was found to inhibit the hERG tail current (K+ channel), hNav1.5 (Na+ channel), and hCav1.2 (Ca2+ channel) in vitro at 8, 117 and 240 times the clinical exposure (based on Cmax), respectively. Overall, the nonclinical safety pharmacology and repeat-dose toxicity data suggest that there will be no ECG effects of eliglustat in humans at plasma levels up to 7-fold clinical Cmax.

Electrocardiographic evaluation

No clinically significant QTc prolonging effect of eliglustat was observed for single doses up to 675 mg.

Prolongation of QT interval was evaluated in a randomised, placebo-controlled and active-controlled (moxifloxacin 400 mg) single-dose crossover study in 47 healthy subjects. In this trial, the upper bound of one-sided 95% confidence interval for the largest placebo-adjusted, baseline-corrected QTcF was below 10 msec. The largest time-matched mean differences (LTMMDs) versus placebo for QTcF interval were 0.7 msec (one-sided 95% CI upper bound of 3.5 msec at Hour 10) and 6.5 msec (one-sided 95% CI upper bound of 9.3 msec at Hour 7) for the single therapeutic (200 mg) and supratherapeutic (800 mg) doses, respectively.

While there was no apparent effect on heart rate, concentration-related increases were observed for the placebo corrected change from baseline in the PR, QRS, and QTc intervals.

Clinical trials

Clinical efficacy and safety

The efficacy and safety of Cerdelga was evaluated in two randomised, controlled pivotal studies (ENGAGE and ENCORE) and one open-label, long-term study (Study 304), in 226 patients with GD1.

Pivotal Study of Cerdelga in Treatment-Naïve GD1 Patients – ENGAGE

ENGAGE was a randomised, double-blind, placebo-controlled, multicentre clinical study evaluating the efficacy and safety of Cerdelga in 40 treatment-naïve GD1 patients 16 years of age or older (median age 30.4 years) with pre-existing splenomegaly and haematological abnormalities. Patients were required to have received no treatment with substrate reduction therapy within 6 months or enzyme replacement therapy within 9 months prior to randomisation; 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 randomised in a 1:1 ratio to receive eliglustat or placebo for the duration of the 9-month blinded primary analysis period. Patients randomised to eliglustat 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 (patients with a plasma trough concentration of <5 ng/mL at Week 2 received a dose increase at Week 4).

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 haemoglobin 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 haemoglobin levels were 128 and 121 g/L, 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 5.

Table 5 - Change from Baseline to Month 9 in Treatment-Naïve Patients with GD1 Receiving Treatment with Cerdelga in ENGAGE

	Placebo (n=20)	Cerdelga (n=20)	Difference (Cerdelga – Placebo) [95% CI]	p-value*
Percentage Change in Spleen Volume MN (%)	2.26	-27.77	-30.0 [-36.8, -23.2]	<0.0001
Absolute Change in Haemoglobin Level (g/L)	-5.4	6.9	12.2 [5.7, 18.8]	0.0006
Percentage Change in Liver Volume MN (%)	1.44	-5.20	-6.64 [-11.37, -1.91]	0.0072

	Placebo (n=20)	Cerdelga (n=20)	Difference (Cerdelga – Placebo) [95% CI]	p-value*
Percentage Change in Platelet Count (%)	-9.06	32.00	41.06 [23.95, 58.17]	<0.0001

MN = Multiples of Normal, CI = confidence interval
* 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 an open-label long term treatment period with Cerdelga (extension phase), all patients with complete data who continued to receive Cerdelga showed further improvements throughout the extension phase. Results (change from baseline) after 18 months, 30 months, and 4.5 years of exposure to Cerdelga on the following endpoints were: mean increase in haemoglobin level (1.1 g/dL) [n=39], 1.4 g/dL [n=35], and 1.4 g/dL [n=12]), mean increase in platelet count [mm3] (58.5% [n=39], 74.6% [n=35], and 86.8% [n=12]), mean reduction in spleen volume [MN] (46.5% [n=38], 54.2% [n=32], and 65.6% [n=13]) and mean reduction of liver volume [MN] (13.7% [n=38], 18.5% [n=32], and 23.4 [n=13]).

Long-Term Clinical Outcomes in Treatment-Naïve Patients – Study 304

Study 304 was a single-arm, open-label, multicentre study of Cerdelga in 26 treatment-naïve adult patients with GD1. Patients were required to have received no treatment with miglustat, enzyme replacement therapy, or corticosteroids for GD1 within 12 months, or bisphosphonates within 3 months prior to enrolment. Twenty-six patients were enrolled, of which 77% (p<0.0001) met the primary endpoint at 12 months, defined as a response in at least 2 of 3 parameters (haemoglobin, platelets, and spleen) that were abnormal at study entry: an increase of ≥5 g/L in haemoglobin; an increase of ≥15% in platelets; and/or a reduction of ≥15% in total spleen volume (based on MRI or spiral CT). Long-term data on visceral and haematological endpoints for up to 19 patients who had an efficacy endpoint assessment at Year 4 and up to 16 patients who had an efficacy endpoint assessment at year 8 are shown in Table 6.

Table 6 - Change from Baseline to Year 4 and 8 in Treatment-Naïve Patients with GD1 Receiving Treatment with Cerdelga in Study 304

	Year	N	Baseline Value (Mean)	Change from Baseline (Mean)	Standard Deviation	95% Confidence Interval	p-value
Spleen Volume	4	18	17.32 MN	-62.5%	11.63	(-68.3, -56.7)	<0.0001
	8	15	17.34 MN	-67.9%	17.11	(-77.3, -58.4)	
Haemoglobin Level	4	19	113.0 g/L	22.7 g/L	14.5	(15.7, 29.7)	<0.0001
	8	16	113.3 g/L	20.8 g/L	1.75	(0.115, 0.301)	
Liver Volume	4	18	1.70 MN	-28.0%	13.80	(-34.9, -21.2)	<0.0001
	8	15	1.60 MN	-31.1%	13.51	(-38.5, -23.6)	
	4	19	68.68x10^9/L	95.1%	89.41	(50.7, 139.4)	0.0003

	Year	N	Baseline Value (Mean)	Change from Baseline (Mean)	Standard Deviation	95% Confidence Interval	p-value
Platelet Count	8	16	67.53 x10^9/L	109.8%	114.73	(48.6, 170.9)	
				MN = Multiples of Normal			

Pivotal Study in Patients Switching from Enzyme Replacement Therapy to Cerdelga - ENCORE

ENCORE was a randomised, open-label, active-controlled, non-inferiority, multicentre clinical study evaluating the safety and efficacy of Cerdelga compared with Cerezyme in 159 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. Patients were randomised 2:1 to receive Cerdelga or Cerezyme for the duration of the 12-month primary analysis period. Enzyme replacement treatment was allowed up to the day before the first dose of Cerdelga. Seventy-five percent of patients randomised to Cerdelga were previously treated with imiglucerase; 21% with velaglucerase alfa and 4% were unreported. Patients randomised 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 (patients with a plasma trough concentration of <5 ng/mL at Weeks 2 and/or 6 received a dose increase at Weeks 4 and/or 8, respectively).

At baseline, mean spleen volumes were 2.6 and 3.2 MN in the Cerezyme and Cerdelga groups, respectively, and liver volumes were 0.9 MN in both groups. Mean haemoglobin levels were 138 and 136 g/L, and platelet counts were 192 and 207 x 10^9/L, respectively.

The primary composite endpoint required stability in all four component domains (haemoglobin 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: haemoglobin level <15 g/L 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: haemoglobin 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.

Mean changes from baseline in the haematological 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 ENCORE

	Cerezyme (N=47) ** Mean [95% CI]	Cerdelga (N=99) Mean [95% CI]
Percentage Change in Spleen Volume MN (%)*	-3.01 [-6.41, 0.40]	-6.17 [-9.54, -2.79]
Absolute Change in Haemoglobin Level (g/L)	0.4 [-1.6, 2.3]	2.1 [-3.5, -0.7]
Percentage Change in Liver Volume MN (%)	3.57 [0.57, 6.58]	1.78 [-0.15, 3.71]
Percentage Change in Platelet Count (%)	2.93 [-0.56, 6.42]	3.79 [0.01, 7.57]

MN = Multiples of Normal, CI = confidence interval
* Excludes patients with a total splenectomy.
**All patients transitioned to Cerdelga treatment after Month 12.

During an open-label long term treatment period with Cerdelga (extension phase) the percentage of patients with complete data meeting the composite stability endpoint was maintained at 84.6% (n=136) after 2 years, 84.4% (n=109) after 3 years and 91.1% (n=45) after 4 years. The majority of extension period discontinuations were due to transition to commercial product from year 3 onwards. Individual disease parameters of spleen volume, liver volume, haemoglobin levels and platelet count remained stable through 4 years.

Clinical experience in CYP2D6 poor metabolisers (PMs) and ultra-rapid metabolisers (URMs)

There is limited experience with Cerdelga treatment of patients who are PMs or URMs. In the primary analysis periods of the three clinical studies, a total of 5 PMs and 5 URMs were treated with Cerdelga. All PMs received 42 mg eliglustat twice daily, and four of these (80%) had an adequate clinical response. The majority of URMs (80%) received a dose escalation to 127 mg eliglustat twice daily, all of which had adequate clinical responses. The one URM who received 84 mg twice daily did not have an adequate response.

The predicted exposures with 84 mg eliglustat once daily in patients who are PMs are expected to be similar to exposures observed with 84 mg eliglustat twice daily in CYP2D6 intermediate metabolisers (IMs). Patients who are URMs may not achieve adequate concentrations to achieve a therapeutic effect. No dosing recommendation for URMs can be given.

Effects on skeletal pathology

In the single-arm, open-label study in treatment-naïve patients (Study 304), improvements in bone marrow infiltration of the femur (as assessed by MRI) were observed in the majority of

patients after 8 years (n=15) of treatment with Cerdelga. The mean total lumbar spine bone mineral density (BMD) increased by 9.9% g/cm^2 (p=0.0176) after 4 years of treatment, and by 12.6% (SD 16.56) after 8 years. Baseline mean (SD) BMD lumbar spine T-score was in the osteopenic range -1.63 (1.07) and reached the normal range after 4 years of treatment -0.88 (1.26) (p=0.0139). After 8 years of treatment, the mean (SD) lumbar spine T-score increased to -0.59 (1.294). Baseline mean (SD) lumbar spine Z-score was -1.21 (0.948) and after 4 years of treatment was -0.48 (1.073) (p=0.0039). After 8 years of treatment, the mean (SD) lumbar spine Z-score was -0.29 (1.088). Femur BMD was in the normal range at baseline and showed little change.

After 9 months of treatment with Cerdelga in the placebo-controlled pivotal study ENGAGE in treatment-naïve patients, bone marrow infiltration by Gaucher cells, as determined by the Total Bone Marrow Burden (BMB) Score (assessed by MRI in lumbar spine and femur), decreased by a mean of 1.1 points in Cerdelga-treated patients (n=19) ; 5 Cerdelga-treated patients (26%) achieved a reduction of at least 2 points in the BMB score after 9 months compared to none in the placebo-treated patients (n=20). After 18 months and 30 months of treatment, BMB score had decreased by a mean of 2.2 (n=18) and 2.7 (n=15) points, respectively, for the patients originally randomized to Cerdelga, compared to a mean decrease of 1 point (n=20) and 0.8 (n=16) in those originally randomized to placebo. Baseline mean (SD) BMD lumbar spine T-score was -1.07 (0.82) in the Cerdelga group (n=17) and -1.12 (1.19) in the placebo group (n=18). After 9 months of treatment, mean lumbar spine T-score was -1.03 (0.83) in the Cerdelga group and -1.22 (1.15) in the placebo group. After 18 months of treatment with Cerdelga in an open-label extension phase, the mean (SD) lumbar spine BMD T-score increased from -1.14 (1.0118) at baseline (n=34) to -0.918 (1.1601) (n=33) in the normal range. After 30 months and 4.5 years of treatment, the T-score further increased to -0.722 (1.1250) (n=27) and -0.533 (0.8031) (n=9), respectively. Mean Z-scores increased in all patients in a similar pattern.

In the pivotal study ENCORE in patients previously treated with enzyme replacement therapy, at baseline, mean lumbar spine and femur BMD were in the normal range and mean BMB Scores were in the moderately affected range for both Cerdelga and Cerezyme groups. After 12 months of treatment, the mean changes in BMD and BMB scores were similar for both arms and were not significantly different from baseline. Lumbar spine and femur BMD T- and Z- scores were maintained within the normal range in patients treated with Cerdelga for up to 4 years.

5.2 PHARMACOKINETIC PROPERTIES

At a given dose of eliglustat, the systemic exposure (C_{max} and AUC) depends on the CYP2D6 phenotype. In CYP2D6 extensive metabolisers (EMs) and intermediate metabolisers (IMs), the eliglustat pharmacokinetics is time-dependent and the systemic exposure increases in a more than dose proportional manner. Following repeated dosing of eliglustat 84 mg twice daily, steady state was reached by 4 days, with an accumulation ratio of 3-fold or less.

Absorption

Median time to reach maximum plasma concentrations occurs between 1.5 to 3 hours after dosing with 84 mg twice daily. The oral bioavailability is low (<5%) due to significant first-pass metabolism. Eliglustat is a substrate of the efflux transporter P-gp. Administration of

eliglustat 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%) without significant red blood cell partitioning. The estimated volume of distribution is 816 L in CYP2D6 intermediate and extensive metabolisers (IMs and EMs), suggesting wide distribution to tissues.

Metabolism

Eliglustat is extensively metabolised 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.

Excretion

Metabolism was the predominant route of elimination, as indicated by the <1% total radioactivity of unchanged free base in urine and faeces. After oral administration, the majority of the administered dose is excreted in urine (41.8%) and faeces (51.4%), mainly as metabolites.

Total body clearance of eliglustat was estimated to be 86 L/h. Mean renal clearance of the unchanged free base was 5.27 L/h.

After repeated oral doses of 84 mg eliglustat twice daily, eliglustat elimination half-life is approximately 4-7 hours in non-PMs and 9 hours in PMs.

Special Populations

CYP2D6 phenotype

Population pharmacokinetic analysis shows that CYP2D6 predicted phenotype based on genotype is the most important factor affecting pharmacokinetic variability. Individuals with a poor CYP2D6 metaboliser predicted phenotype (approximately 5 to 10% of the population) exhibit higher eliglustat concentrations than intermediate or extensive CYP2D6 metabolisers.

In poor metabolisers (PMs), the systemic exposure following 84 mg twice daily at steady state was 7 to 9-fold higher compared to extensive metabolisers (EMs). Oral dosing of 84 mg twice daily is not recommended in CYP2D6 poor metabolisers (PMs).

Gender, Elderly, Paediatric Patients

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

Hepatic Impairment

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} and 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. Simulated 84 mg twice daily doses of Cerdelga with a physiologically-based PK model showed C_{max} and AUC_{0-12} 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 (see section 4.3 - Contraindications).

Steady state pharmacokinetic 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 section 4.3-Contraindications).

Renal Impairment

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 were similar in CYP2D6 EMs with severe renal impairment and healthy CYP2D6 EMs.

Limited or no data were available in patients with end stage renal disease and in CYP2D6 IMs or PMs with severe renal impairment.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Eliglustat was not mutagenic in a standard battery of genotoxicity tests.

Carcinogenicity

Eliglustat did not show any carcinogenic potential in standard lifetime bioassays in mice and rats. Exposures in the carcinogenicity studies were approximately 4-fold and 3-fold, respectively, greater than the mean predicted human eliglustat exposure (based on AUC).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Inactive ingredients: microcrystalline cellulose, lactose monohydrate, hypromellose and glycerol dibehenate.

Capsule shell: gelatin, candurin silver fine (E555 and E171), iron oxide yellow (E172), indigo carmine (E132).

Printing ink: shellac, iron oxide black (E172), propylene glycol, ammonium hydroxide.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Cerdelga is supplied in blister packs. Each pack contains 56 hard capsules in blister wallets of 14 hard capsules each.

Blister lidding material is aluminium foil; forming material is composed of PETG/cyclic olefin copolymer/PETG with a PCTFE film.

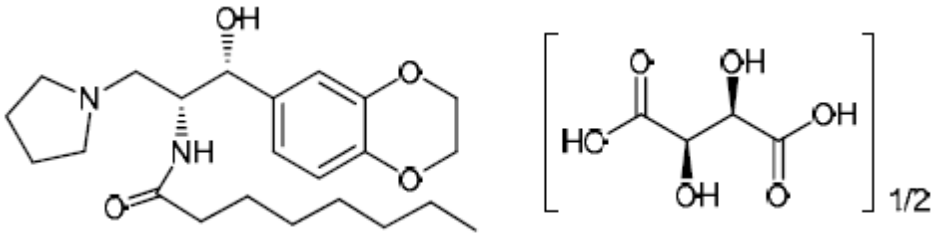
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical structure of eliglustat tartrate is:



Molecular Formula: $C_{23}H_{36}N_2O_4 + ½ (C_4H_6O_6)$

Molecular Weight: 479.59 g/mol

Chemical Name: Octanamide, *N*-[(*1R,2R*)-2-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-hydroxy-1-(1-pyrrolidinylmethyl)ethyl]-, (*2R,3R*)-2,3-dihydroxybutanedioate (2:1)

CAS number

CAS Registry Number: 928659-70-5.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

sanofi-aventis australia pty ltd
International Tower 3, Level 23
300 Barangaroo Avenue
Sydney NSW 2000
Freecall: 1800 818 806
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

17 February 2015

10 DATE OF REVISION

28 May 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Sponsor details updated