

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Cerdelga 84 mg capsules, hard

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 84.4 mg of eliglustat (as tartrate).

### Excipient(s) with known effect:

Each capsule contains 106 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Capsule, hard.

Capsule with pearl blue-green opaque cap and pearl white opaque body with “GZ02” printed in black on the body of 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), who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs).

### 4.2 Posology and method of administration

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

#### Posology

The recommended dose is 84 mg eliglustat twice daily in CYP2D6 intermediate metabolisers (IMs) and extensive metabolisers (EMs). The recommended dose is 84 mg eliglustat once daily in CYP2D6 poor metabolisers (PMs). If a dose is missed, the prescribed dose should be taken at the next scheduled time; the next dose should not be doubled.

The capsules may be taken with or without food. Consumption of grapefruit or its juice should be avoided (see section 4.5).

#### Special populations

##### *CYP2D6 ultra-rapid metabolisers (URMs) and indeterminate metabolisers*

Cerdelga should not be used in patients who are CYP2D6 ultra-rapid metabolisers (URMs) or indeterminate metabolisers (see section 4.4).

#### *Patients with hepatic impairment*

Cerdelga has not been studied in patients with hepatic impairment. Therefore, no dose recommendations can be made.

#### *Patients with renal impairment*

Cerdelga has not been studied in patients with renal impairment. Therefore, no dose recommendations can be made.

#### *Elderly patients (≥65 years)*

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 elderly patients and younger patients.

#### *Paediatric population*

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

#### Method of administration

Cerdelga is to be taken orally. The capsules should be swallowed whole, preferably with water, and should not be crushed, dissolved, or opened.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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, and patients who are CYP2D6 poor metabolisers (PMs) taking a strong CYP3A inhibitor. Use of Cerdelga under these conditions results in substantially elevated eliglustat plasma concentrations (see section 4.4 and 4.5).

### **4.4 Special warnings and precautions for use**

#### Initiation of therapy: CYP2D6 genotyping

Before initiation of treatment with Cerdelga, patients should be genotyped for CYP2D6 to determine the CYP2D6 metaboliser status (see section 4.2, Special populations).

#### 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, and in patients who are 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 (see section 4.5). Although no significant QTc increases were seen in a thorough QT study in healthy volunteers, based on PK/PD modelling, eliglustat plasma concentrations 11-fold the predicted human C<sub>max</sub> are predicted to cause mild increases in the PR, QRS, and QTc intervals (see section 5.1, Electrocardiographic evaluation).

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

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

#### 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 Cerdelga should be avoided in patients with cardiac disease (congestive heart failure, recent acute myocardial infarction, bradycardia, heart block, ventricular arrhythmia), long QT syndrome, and in combination with Class IA (e.g. quinidine) and Class III (e.g. amiodarone, sotalol) antiarrhythmic medicinal products.

#### Monitoring of clinical response

Some treatment-naïve patients showed less than 20% spleen volume reduction (sub-optimal results) after 9 months of treatment (see section 5.1). For these patients, monitoring for further improvement or an alternative treatment modality should be considered.

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.

#### Lactose

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

### **4.5 Interaction with other medicinal products and other forms of interaction**

Eliglustat is metabolised primarily by CYP2D6 and to a lesser extent by CYP3A4. Concomitant administration of substances affecting CYP2D6 or CYP3A4 activity may alter eliglustat plasma concentrations. Eliglustat is an inhibitor of P-gp and CYP2D6 *in vitro*; concomitant administration of eliglustat with P-gp or CYP2D6 substrate substances may increase the plasma concentration of those substances.

The list of substances in section 4.5 is not an inclusive list and the prescriber is advised to consult the SmPC of all other prescribed medicinal products 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, and in patients who are CYP2D6 poor metabolisers (PMs) taking a strong CYP3A inhibitor (see section 4.3). Use of Cerdelga under these conditions results in substantially elevated eliglustat plasma concentrations.

#### *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 7.3- and 8.9-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, moclobemide, mirabegron, cinacalcet, dronedarone) would increase eliglustat exposure approximately up to 4-fold. Caution should be used with moderate CYP2D6 inhibitors in IMs and EMs.

## *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 400 mg once daily doses of ketoconazole, a strong inhibitor of CYP3A, resulted in a 3.8 and 4.3-fold increase in eliglustat  $C_{\max}$  and  $AUC_{0-12}$ , respectively; similar effects would be expected for other strong inhibitors of CYP3A (e.g. clarithromycin, ketoconazole, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir). 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 concomitant use of moderate CYP3A inhibitors (e.g. erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine) would increase eliglustat exposure approximately up to 3-fold. Caution should be used with moderate CYP3A inhibitors in IMs and EMs.

### *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, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir) would increase the  $C_{\max}$  and  $AUC_{0-24}$  of eliglustat 4.3- and 6.2-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, ciprofloxacin, fluconazole, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine) would increase the  $C_{\max}$  and  $AUC_{0-24}$  of eliglustat 2.4- and 3.0-fold, respectively. Use of a moderate CYP3A inhibitor 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. Consumption of grapefruit or its juice should be avoided.

### *Agents that may decrease eliglustat exposure*

#### *Strong CYP3A inducers*

After repeated 127 mg twice daily doses of eliglustat in non-PMs, concomitant administration of repeated 600 mg once 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 a strong CYP3A inducer (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, rifabutin and St. John's wort) with eliglustat is not recommended in IMs, EMs and PMs.

#### Agents whose exposure may be increased by eliglustat

##### P-gp substrates

After a single 0.25 mg dose of digoxin, a P-gp substrate, concomitant administration of 127 mg twice daily doses of eliglustat resulted in a 1.7- and 1.5-fold increase in digoxin  $C_{max}$  and  $AUC_{last}$ , respectively. Lower doses of substances which are P-gp substrates (e.g. digoxin, colchicine, dabigatran, phenytoin, pravastatin) may be required.

##### CYP2D6 substrates

After a single 50 mg dose of metoprolol, a CYP2D6 substrate, concomitant administration of repeated 127 mg twice daily doses of eliglustat resulted in a 1.5- and 2.1-fold increase in metoprolol  $C_{max}$  and AUC, respectively. Lower doses of medicinal products that are CYP2D6 substrates may be required. These include certain antidepressants (tricyclic antidepressants, e.g. nortriptyline, amitriptyline, imipramine, and desipramine), phenothiazines, dextromethorphan and atomoxetine).

## **4.6 Fertility, pregnancy and lactation**

### Pregnancy

There are no or limited amount of data from the use of eliglustat in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is recommended to avoid the use of Cerdelga during pregnancy.

### Breast-feeding

It is unknown whether eliglustat or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of eliglustat in milk (see section 5.3). A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Cerdelga therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

### Fertility

Effects on testes and reversible inhibition of spermatogenesis were observed in rats (see section 5.3). The relevance of these findings for humans is not known.

## **4.7 Effects on ability to drive and use machines**

Cerdelga has no or negligible influence on the ability to drive and use machines.

## **4.8 Undesirable effects**

### Summary of the safety profile

The majority of adverse reactions are mild and transient. The most frequently 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.

### Tabulated list of adverse reactions

The overall adverse reaction profile of Cerdelga 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), one 8-year, long term 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 duration of 3.5 years (up to 9.3 years).

Adverse reactions are ranked by system organ class and frequency ([very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare

(<1/10,000)). All adverse reactions reported in >2% of the patients are presented in Table 1. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

**Table 1: Tabulated list of adverse reactions**

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

A cut-off of >2% was applied

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

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

## **4.9 Overdose**

The highest eliglustat plasma concentration observed 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 treatment and supportive care.

## **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

Eliglustat is a potent and specific inhibitor of glucosylceramide synthase, and acts as a substrate reduction therapy (SRT) for GD1. SRT aims to reduce the rate of synthesis of the major substrate glucosylceramide (GL-1) to match its impaired rate of catabolism in patients with GD1, thereby preventing glucosylceramide accumulation and alleviating clinical manifestations.

#### Pharmacodynamic effects

In clinical trials in treatment-naïve GD1 patients, plasma GL-1 levels were elevated in the majority of these patients and decreased upon Cerdelga 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 Cerdelga treatment), plasma GL-1 levels were normal in most patients and decreased upon Cerdelga treatment.

### Clinical efficacy and safety

The recommended dosing regimens (see section 4.2) are based on modelling, either of PK/PD data from the dose-titration regimens applied in the clinical studies for IMs and EMs, or physiologically-based PK data for PMs.

#### *Pivotal study of Cerdelga in treatment-naïve GD1 patients – study 02507(ENGAGE)*

Study 02507 was a randomized, double-blind, placebo-controlled, multicenter clinical study in 40 patients with GD1. In the Cerdelga group 3 (15%) patients received a starting dose of 42 mg eliglustat 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.

**Table 2: Change from baseline to Month 9 (primary analysis period) in treatment-naïve patients with GD1 receiving treatment with Cerdelga in study 02507**

	Placebo* (n=20) <sup>a</sup>	Cerdelga (n=20) <sup>a</sup>	Difference (Cerdelga – Placebo) [95% CI]	p value <sup>b</sup>
Percentage Change in Spleen Volume MN (%) (primary endpoint)	2.26	-27.77	-30.0 [-36.8, -23.2]	<0.0001
Absolute Change in Haemoglobin Level (g/dL) (secondary endpoint)	-0.54	0.69	1.22 [0.57, 1.88]	0.0006
Percentage Change in Liver Volume MN (%) (secondary endpoint)	1.44	-5.20	-6.64 [-11.37, -1.91]	0.0072
Percentage Change in Platelet Count (%) (secondary endpoint)	-9.06	32.00	41.06 [23.95, 58.17]	<0.0001

MN = Multiples of Normal, CI = confidence interval

<sup>a</sup> 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 12.8 and 12.1 g/dL, and platelet counts were 78.5 and 75.1 x 10<sup>9</sup>/L, respectively.

<sup>b</sup> Estimates and p-values are based on an ANCOVA model

\* All patients transitioned to Cerdelga treatment after Month 9.

During the 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: absolute change in haemoglobin level (g/dL) 1.1 (1.03) [n=39], 1.4 (0.93) [n=35], and 1.4 (1.31) [n=12]; mean increase in platelet count (mm<sup>3</sup>) 58.5% (40.57%) [n=39], 74.6% (49.57%) [n=35], and 86.8% (54.20%) [n=12]; mean reduction in spleen volume (MN) 46.5% (9.75%) [n=38], 54.2% (9.51%) [n=32], and 65.6% (7.43%) [n=13]; and mean reduction in liver volume (MN) 13.7% (10.65%) [n=38], 18.5% (11.22%) [n=32], and 23.4% (10.59%) [n=13].

#### *Long-term clinical outcomes in treatment-naïve GD1 patients – study 304*

Study 304 was a single-arm, open-label, multicenter study of Cerdelga in 26 patients. Nineteen patients completed 4 years of treatment. Fifteen (79%) of these patients received a dose escalation to 84 mg eliglustat twice daily; 4 (21%) patients continued to receive 42 mg twice daily.

Eighteen patients completed 8 years of treatment. One patient (6%) received a further dose escalation to 127 mg twice daily. Fourteen (78%) continued on 84 mg Cerdelga twice daily. Three (17%) patients continued to receive 42 mg twice daily. Sixteen patients had an efficacy endpoint assessment at year 8.

Cerdelga showed sustained improvements in organ volume and haematological parameters over the 8 year treatment period (see Table 3).



**Table 3: Change from baseline to year 8 in study 304**

	N	Baseline Value (Mean)	Change from Baseline (Mean)	Standard Deviation
Spleen Volume (MN)	15	17.34	-67.9%	17.11
Haemoglobin Level (g/dL)	16	11.33	2.08	1.75
Liver Volume (MN)	15	1.60	-31.0%	13.51
Platelet Count (x10 <sup>9</sup> /L)	16	67.53	109.8%	114.73

MN = Multiples of Normal

*Pivotal study of Cerdelga in GD1 patients switching from ERT– Study 02607 (ENCORE)*

Study 02607 was a randomized, open-label, active-controlled, non-inferiority, multicenter clinical study in 159 patients previously stabilised with ERT. In the Cerdelga group 34 (32%) patients received a dose escalation to 84 mg eliglustat twice daily and 51 (48%) to 127 mg twice daily during the 12-month primary analysis period, and 21 (20%) patients continued to receive 42 mg twice daily.

Based on the aggregate data from all doses tested in this study, Cerdelga met the criteria set in this study to be declared non-inferior to Cerezyme (imiglucerase) in maintaining patient stability. After 12 months of treatment, the percentage of patients meeting the primary composite endpoint (composed of all four components mentioned in Table 4) was 84.8% [95% confidence interval 76.2% - 91.3%] for the Cerdelga group compared to 93.6% [95% confidence interval 82.5% - 98.7%] for the Cerezyme group. 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.

There were no clinically meaningful differences between groups for any of the four individual disease parameters (see Table 4).

**Table 4: Changes from baseline to Month 12 (primary analysis period) in patients with GD1 switching to Cerdelga in study 02607**

	Cerezyme (N=47)** Mean [95% CI]	Cerdelga (N=99) Mean [95% CI]
<b>Spleen Volume</b>		
Percentage of Patients with stable spleen volume* <sup>a</sup>	100%	95.8%
Percentage Change in Spleen Volume MN (%)*	-3.01 [-6.41, 0.40]	-6.17 [-9.54, -2.79]
<b>Haemoglobin Level</b>		
Percentage of Patients with stable haemoglobin level <sup>a</sup>	100%	94.9%
Absolute Change in Haemoglobin Level (g/dL)	0.038 [-0.16, 0.23]	-0.21 [-0.35, -0.07]
<b>Liver Volume</b>		
Percentage of Patients with stable liver volume <sup>a</sup>	93.6%	96.0%
Percentage Change in Liver Volume MN (%)	3.57 [0.57, 6.58]	1.78 [-0.15, 3.71]
<b>Platelet Count</b>		
Percentage of Patients with stable platelet count <sup>a</sup>	100%	92.9%
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 52 weeks

<sup>a</sup> The stability criteria based on changes between baseline and 12 months: haemoglobin level ≤1.5 g/dL decrease, platelet count ≤25% decrease, liver volume ≤20% increase, and spleen volume ≤25% increase.

All patient number (N)= Per Protocol Population

During the 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 phase 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 (see Table 5).

**Table 5: Changes from Month 12 (primary analysis period) to Month 48 in patients with GD1 in the Long Term Treatment Period on Cerdelga in study 02607**

	Year 2		Year 3		Year 4	
	Cerezyme /Cerdelga <sup>a</sup> Mean [95% CI]	Cerdelga <sup>b</sup> Mean [95% CI]	Cerezyme /Cerdelga <sup>a</sup> Mean [95% CI]	Cerdelga <sup>b</sup> Mean [95% CI]	Cerezyme /Cerdelga <sup>a</sup> Mean [95% CI]	Cerdelga <sup>b</sup> Mean [95% CI]
Patients at start of year (N)	51	101	46	98	42	96
Patients at end of year (N)	46	98	42	96	21	44
Patients with available data (N)	39	97	16	93	3	42
<b>Spleen Volume</b>						
Patients with stable spleen volume (%)*	31/33 (93.9) [0.798, 0.993]	69/72 (95.8) [0.883, 0.991]	12/12 (100.0) [0.735, 1.000]	65/68 (95.6) [0.876, 0.991]	2/2 (100.0) [0.158, 1.000]	28/30 (93.3) [0.779, 0.992]
Change in Spleen Volume MN (%)*	-3.946[-8.80, 0.91]	-6.814[-10.61, -3.02]	-10.267[-20.12, -0.42]	-7.126[-11.70, -2.55]	-27.530[-89.28, 34.22]	-13.945[-20.61, -7.28]
<b>Haemoglobin Level</b>						
Patients with stable haemoglobin level (%)	38/39 (97.4) [0.865, 0.999]	95/97 (97.9) [0.927, 0.997]	16/16 (100.0) [0.794, 1.000]	90/93 (96.8) [0.909, 0.993]	3/3 (100.0) (0.292, 1.000)	42/42 (100.0) [0.916, 1.000]
Change from baseline in Haemoglobin Level (g/dL)	0.034[-0.31, 0.38]	-0.112[-0.26, 0.04]	0.363[-0.01, 0.74]	-0.103[-0.27, 0.07]	0.383[-1.62, 2.39]	0.290[0.06, 0.53]
<b>Liver Volume</b>						
Patients with stable liver volume (%)	38/39 (97.4) (0.865, 0.999)	94/97 (96.9) (0.912, 0.994)	15/16 (93.8) [0.698, 0.998]	87/93 (93.5) (0.865, 0.976)	3/3 (100.0) [0.292, 1.000]	40/42 (95.2) [0.838, 0.994]
Change from baseline in Liver Volume MN (%)	0.080[-3.02, 3.18]	2.486[0.50, 4.47]	-4.908[-11.53, 1.71]	3.018[0.52, 5.52]	-14.410[-61.25, 32.43]	-1.503[-5.27, 2.26]
<b>Platelet Count</b>						
Patients with stable platelet count (%)	33/39 (84.6) [0.695, 0.941]	92/97 (94.8) [0.884, 0.983]	13/16 (81.3) [0.544, 0.960]	87/93 (93.5) [0.865, 0.976]	3/3 (100.0) [0.292, 1.000]	40/42 (95.2) [0.838, 0.994]
Change in Platelet Count (%)	-0.363[-6.60, 5.88]	2.216[-1.31, 5.74]	0.719[-8.20, 9.63]	5.403[1.28, 9.52]	-0.163[-35.97, 35.64]	7.501[1.01, 13.99]
<b>Composite Stability Endpoint</b>						
Patients who are Stable on Cerdelga (%)	30/39 (76.9) [0.607, 0.889]	85/97 (87.6) [0.794, 0.934]	12/16 (75.0) [0.476, 0.927]	80/93 (86.0) [0.773, 0.923]	3/3 (100.0) [0.292, 1.000]	38/42 (90.5) [0.774, 0.973]

MN = Multiples of Normal, CI = confidence interval

\* Excludes patients with a total splenectomy.

a Cerezyme/Cerdelga - Originally Randomized to Cerezyme

b Cerdelga - Originally Randomized to Cerdelga

### 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

After 9 months of treatment, in Study 02507, 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) compared to no change in patients receiving placebo (n=20). Five Cerdelga-treated patients (26%) achieved a reduction of at least 2 points in the BMB score.

After 18 and 30 months of treatment, BMB score had decreased by a mean 2.2 points (n=18) and 2.7 (n=15), respectively for the patients originally randomised to Cerdelga, compared to a mean decrease of 1 point (n=20) and 0.8 (n=16) in those originally randomised to placebo.

After 18 months of Cerdelga treatment in the open-label extension phase, the mean (SD) lumbar spine Bone Mineral Density 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.

Results of study 304 indicate that skeletal improvements are maintained or continue to improve during at least 8 years of treatment with Cerdelga.

In study 02607, 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.

### Electrocardiographic evaluation

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

Heart-rate corrected QT interval using Fridericia's correction (QTcF) was evaluated in a randomized, placebo and active (moxifloxacin 400 mg) controlled cross-over, single-dose study in 47 healthy subjects. In this trial with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo-adjusted, baseline-corrected QTcF was below 10 msec, the threshold for regulatory concern. 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. Based on PK/PD modelling, eliglustat plasma concentrations 11-fold the predicted human  $C_{max}$  are expected to cause mean (upper bound of the 95% confidence interval) increases in the PR, QRS, and QTcF intervals of 18.8 (20.4), 6.2 (7.1), and 12.3 (14.2) msec, respectively.

### Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Cerdelga in all subsets of the paediatric population in Gaucher disease Type 2 (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with Cerdelga in the subsets of the paediatric population from 24 months to less than 18 years in Gaucher disease Type 1 and Type 3 (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

### Absorption

Median time to reach maximum plasma concentrations occurs between 1.5 to 3 hours after dosing, with low oral bioavailability (<5%) due to significant first-pass metabolism. Eliglustat is a substrate of the efflux transporter P-gp. Food does not have a clinically relevant effect on eliglustat pharmacokinetics. 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. Oral dosing of 84 mg eliglustat once daily has not been studied in CYP2D6 poor metabolisers (PMs).

### Distribution

Eliglustat is moderately bound to human plasma proteins (76 to 83%) and is mainly distributed in plasma. After intravenous administration, the volume of distribution was 816 L, suggesting wide distribution to tissues in humans. Nonclinical studies demonstrated a wide distribution of eliglustat to tissues, including bone marrow.

### Biotransformation

Eliglustat is extensively metabolized with high clearance, mainly by CYP2D6 and to a lesser extent CYP3A4. Primary metabolic pathways of eliglustat involve sequential oxidation of the octanoyl moiety followed by oxidation of the 2,3-dihydro-1,4-benzodioxane moiety, or a combination of the two pathways, resulting in multiple oxidative metabolites.

### Elimination

After oral administration, the majority of the administered dose is excreted in urine (41.8%) and faeces (51.4%), mainly as metabolites. After intravenous administration, eliglustat total body clearance was 86 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.

### Characteristics in specific groups

#### *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 poor metaboliser predicted phenotype (approximately 5 to 10% of the population) exhibit higher eliglustat concentrations than intermediate or extensive CYP2D6 metabolisers.

#### *Gender, body weight, age, and race*

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

## 5.3 Preclinical safety data

The principal target organs for eliglustat in toxicology studies are the GI tract, lymphoid organs, the liver in rat only and, in the male rat only, the reproductive system. 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 using total plasma exposure and 1- to 2-fold using unbound (free fraction) plasma exposures.

Eliglustat did not have effects on CNS or respiratory functions. Concentration-dependent cardiac effects were observed in nonclinical studies: inhibition of human cardiac ion channels, including potassium, sodium, and calcium, at concentrations  $\geq$  7-fold of predicted human  $C_{max}$ ; sodium ion channel-mediated effects in an ex-vivo electrophysiology study in dog Purkinje fibres (2-fold of predicted human unbound plasma  $C_{max}$ ); and increases in QRS and PR intervals in dog telemetry and cardiac conduction studies in anaesthetised dogs, with effects seen at concentrations 14-fold of predicted human total plasma  $C_{max}$ , or 2-fold of predicted human unbound plasma  $C_{max}$ .

Eliglustat was not mutagenic in a standard battery of genotoxicity tests and 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 greater in mice and rats, respectively, than the mean predicted human eliglustat total plasma exposure, or less than 1-fold using unbound plasma exposure.

In mature male rats, no effects on sperm parameters were observed at systemically non-toxic doses. Reversible inhibition of spermatogenesis was observed in the rat at 10-fold of predicted human exposure based on AUC, a systemically toxic dose. In rat repeated dose toxicity studies, seminiferous epithelial degeneration and segmental hypoplasia of the testes was seen at 10-fold of predicted human exposure based on AUC.

Placental transfer of eliglustat and its metabolites was shown in the rat. At 2 and 24 hours post-dose, 0.034 % and 0.013 % of labelled dose was detected in foetal tissue, respectively.

At maternal toxic doses in rats, foetuses showed a higher incidence of dilated cerebral ventricles, abnormal number of ribs or lumbar vertebrae, and many bones showed poor ossification. Embryofoetal development in rats and rabbits was not affected up to clinically relevant exposure (based on AUC).

A lactation study in the rat showed that 0.23% of labelled dose was transferred to pups during 24 hours post-dose, indicating milk excretion of eliglustat and/or its related materials.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Capsule contents:

Microcrystalline cellulose  
Lactose monohydrate  
Hypromellose  
Glycerol dibehenate

#### Capsule shell:

Gelatin  
Potassium aluminium silicate (E555)  
Titanium dioxide (E171)  
Yellow iron oxide (E172)  
Indigotine (E132)

#### Printing ink:

Shellac glaze  
Black iron oxide (E172)  
Propylene glycol  
Ammonium hydroxide 28%

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years

#### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

#### **6.5 Nature and contents of container**

PETG/COC.PETG/PCTFE-aluminium blister

Each blister wallets contains 14 hard capsules.  
Each pack contains 14, 56 or 196 hard capsules.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal**

Any unused product or waste material should be disposed of in accordance with local requirements.

### **7. MARKETING AUTHORISATION HOLDER**

Genzyme Europe B.V., Gooimeer 10, 1411DD, Naarden, The Netherlands

### **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/14/974/001 56 capsules  
EU/1/14/974/002 196 capsules  
EU/1/14/974/003 14 capsules

### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 19 January 2015

### **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **ANNEX II**

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## **A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

### Name and address of the manufacturer responsible for batch release

Genzyme Ireland, Ltd  
IDA Industrial Park  
Old Kilmeaden Road,  
Waterford Ireland

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

### **• Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

### **• Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

### **• Additional risk minimisation measures**

Prior to launch of Cerdelga in each Member State the Marketing Authorisation Holder (MAH) must agree the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Cerdelga is marketed, all healthcare professionals who are expected to prescribe Cerdelga are provided with a prescriber guide.



The prescriber guide shall contain the following key elements:

- Cerdelga is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1). ***It is not intended to be used*** in patients with Gaucher disease type 2 or type 3 (GD2 or GD3).
- Before initiation of treatment with Cerdelga, patients should be genotyped for CYP2D6 to determine the CYP2D6 metaboliser status. Cerdelga is indicated in patients who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs).
- The recommended dose is 84 mg eliglustat twice daily in CYP2D6 intermediate metabolisers (IMs) and extensive metabolisers (EMs). The recommended dose is 84 mg eliglustat once daily in CYP2D6 poor metabolisers (PMs).
- Patients should be informed that consumption of grapefruit or its juice should be avoided.
- Eliglustat is contraindicated in patients who are CYP2D6 Intermediate Metabolisers or Extensive Metabolisers who are taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor. Eliglustat is also contraindicated in patients who are CYP2D6 poor metabolisers taking a strong CYP3A inhibitor. Use of eliglustat under these conditions results in substantially elevated plasma concentrations of eliglustat. This may cause mild increases in the PR, QRS, and QTc intervals.
- Use of eliglustat with strong CYP3A inducers substantially decreases the exposure to eliglustat, which may reduce the therapeutic effectiveness; therefore concomitant administration is not recommended.

The MAH shall ensure that in each Member State where Cerdelga is marketed, all patients who are prescribed Cerdelga are provided with a patient alert card. The patient alert card shall contain the following key elements:

Information for healthcare professionals:

- This patient is using eliglustat (Cerdelga) for the treatment of Gaucher Disease type 1.
- Eliglustat should not be used concomitantly with medicines that may have an impact on liver enzymes that play a role in the metabolism of eliglustat.
- Using eliglustat together with such products may either make eliglustat less effective, or it may increase the eliglustat levels in the patient's blood.

Information for the patient:

- Always consult the doctor who prescribed eliglustat before you start using other medicines.
- Do not consume grapefruit products.

- **Obligation to conduct post-authorisation measure**

The MAH shall complete, within the stated timeframe, the below measure:

Description	Due date
In order to investigate the long-term safety of eliglustat in patients prescribed eliglustat, the MAH is to create a sub-registry to the International Collaborative Gaucher Group (ICGG) Gaucher Registry to collect safety data according to an agreed protocol.	Reports from the sub-registry are to be submitted with each PSUR.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Cerdelga 84 mg hard capsules  
eliglustat

**2. STATEMENT OF ACTIVE SUBSTANCE**

Each capsule contains 84 mg of eliglustat (as tartrate)

**3. LIST OF EXCIPIENTS**

Contains lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

14 hard capsules  
56 hard capsules  
196 hard capsules

**5. METHOD AND ROUTE OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNINGS, IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Genzyme Europe B.V.  
Gooimeer 10  
1411DD  
Naarden  
The Netherlands

**12. MARKETING AUTHORISATION NUMBERS**

EU/1/14/974/001 56 capsules  
EU/1/14/974/002 196 capsules  
EU/1/14/974/003 14 capsules

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Cerdelga

**17. UNIQUE IDENTIFIER – 2D BARCODE**

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**INTERMEDIATE PACKAGING FOR SINGLE BLISTER:SLEEVE**

**1. NAME OF THE MEDICINAL PRODUCT**

Cerdelga 84 mg hard capsules  
eliglustat

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each capsule contains 84 mg of eliglustat (as tartrate)

**3. LIST OF EXCIPIENTS**

Contains lactose. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

14 hard capsules

**5. METHOD AND ROUTE OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

Press down at 1 and at the same time pull at 2.



**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNINGS, IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Genzyme Europe B.V.  
Gooimeer 10  
1411DD  
Naarden  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER**

EU/1/14/974/001 56 capsules  
EU/1/14/974/002 196 capsules  
EU/1/14/974/003 14 capsules

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Cerdelga

**17. UNIQUE IDENTIFIER – 2D BARCODE**

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER / WALLET**

**1. NAME OF THE MEDICINAL PRODUCT**

Cerdelga 84 mg hard capsules  
eliglustat

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Genzyme Europe B.V.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**



**B. PACKAGE LEAFLET**

## Package leaflet: Information for the patient

### Cerdelga 84 mg capsules, hard eliglustat

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

#### **Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Cerdelga is and what it is used for
2. What you need to know before you take Cerdelga
3. How to take Cerdelga
4. Possible side effects
5. How to store Cerdelga
6. Contents of the pack and other information

#### **1. What Cerdelga is and what it is used for**

Cerdelga is a medicine used for the long term treatment of adult patients with Gaucher disease type 1.

Gaucher disease type 1 is a rare, inherited condition in which a substance called glucosylceramide is not effectively broken down by your body. As a result glucosylceramide builds up in your spleen, liver and bones. The build-up prevents these organs from working properly. Cerdelga contains the active substance eliglustat which decreases the production of glucosylceramide, thereby preventing its build-up. In turn this helps your affected organs to work better.

People differ in the speed that their body breaks down this medicine. As a result the amount of this medicine in the blood can differ between patients which could affect how a patient would respond. Cerdelga is meant to be used in patients whose body breaks down this medicine at normal speed (known as intermediate metabolisers and extensive metabolisers) or slow speed (known as poor metabolisers). Your doctor will determine if Cerdelga is suitable for you before you start taking it, using a simple laboratory test.

Gaucher disease type 1 is a lifelong condition and you must continue to take this medicine as prescribed by your doctor to gain the maximum benefit from your medicine.

#### **2. What you need to know before you take Cerdelga**

##### **Do not take Cerdelga**

- If you are allergic to eliglustat or any of the other ingredients of this medicine (listed in section 6).
- If you break down Cerdelga at a normal speed and use medicines known as strong or moderate CYP2D6 inhibitors (examples are quinidine and terbinafine) used in combination with strong or moderate CYP3A inhibitors (examples are erythromycin and itraconazole). The

combination of these medicines will interfere with your body's ability to break down Cerdelga and this can result in higher levels of the active substance in your blood (see the section 'Other medicines and Cerdelga' for an expanded list of medicines).

- If you break down Cerdelga at a slow speed and use medicines known as strong CYP3A inhibitors (for example itraconazole). Medicines of this type will interfere with your body's ability to break down Cerdelga and this can result in higher levels of the active substance in your blood (see the section 'Other medicines and Cerdelga' for an expanded list of medicines).

### **Warnings and precautions**

Talk to your doctor or pharmacist before taking Cerdelga, if you:

- are currently treated, or about to start treatment with any of the medicines listed in section '*Other medicines and Cerdelga.*'
- have had a heart attack or heart failure.
- have a slow heart rate.
- have an irregular, or abnormal heart beat, including a heart condition called long QT syndrome.
- have any other heart problems.
- are taking an antiarrhythmic medicine (used to treat irregular heart beat) like quinidine, amiodarone or sotalol.

### **Children and adolescents**

Cerdelga has not been tested in children and adolescents under 18 years of age. Do not give this medicine to children or adolescents.

### **Other medicines and Cerdelga**

Please tell your doctor or pharmacist if you are using, or have recently used, or might use, any other medicines.

### **Medicines that must not be taken in combination with each other and Cerdelga**

Cerdelga must not be used with certain type of medicines. These medicines can interfere with your body's ability to break down Cerdelga and this can result in higher levels of Cerdelga in your blood. These medicines are known as strong or moderate CYP2D6 inhibitors and strong or moderate CYP3A inhibitors. There are many medicines in these categories and depending on how your body breaks down Cerdelga the effects may differ from person to person. Please speak to your doctor regarding these medicines before you start taking Cerdelga. Your doctor will determine which medicines you can use based on how fast your body breaks down eliglustat.

### **Medicines that may increase the level of Cerdelga in the blood such as:**

- paroxetine, fluoxetine, fluvoxamine, duloxetine, bupropion, moclobemide – **antidepressants** (used to treat depression)
- dronedarone, quinidine, verapamil – **antiarrhythmic medicines** (used to treat irregular heartbeat)
- ciprofloxacin, clarithromycin, erythromycin, telithromycin – **antibiotics** (used to treat infections)
- terbinafine, itraconazole, fluconazole, posaconazole, voriconazole – **antifungals** (used to treat fungal infections)
- mirabegron – used to treat overactive bladders
- cinacalcet – **calcimimetic** (used in some dialysis patients and specific cancers)
- atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, ritonavir, saquinavir, tipranavir – **antiretrovirals** (used to treat HIV)
- cobicistat – used to improve the effects of antiretrovirals (used to treat HIV)
- aprepitant – **antiemetic** (used to reduce vomiting)
- diltiazem – **antihypertensive** (used to increase blood flow and decrease heart rate)
- conivaptan – **diuretic** (used to increase low blood sodium levels)
- boceprevir, telaprevir – **antiviral** (used to treat Hepatitis C)
- imatinib – **anticancer** (used to treat cancer)

- amlopidine, ranolazine – used to treat angina pectoris
- cilostazol – used to treat cramp-like pain in your legs when you walk caused by insufficient blood supply in your legs
- isoniazid – used to treat tuberculosis.
- cimetidine, ranitidine – **antacids** (used to treat indigestion)
- goldenseal – (also known as *Hydrastis canadensis*) a herbal preparation obtained without a prescription, used as a digestive aid.

**Medicines that may decrease the level of Cerdelga in the blood:**

- rifampicin, rifabutin – **antibiotics** (used to treat infections)
- carbamazepine, phenobarbital, phenytoin –**anti-epileptics** (used to treat epilepsy and seizures)
- St. John’s wort – (also known as *Hypericum perforatum*) a herbal preparation obtained without a prescription, used to treat **depression** and other conditions

**Cerdelga may increase the level of the following types of medicines in the blood:**

- dabigatran – **anticoagulant** (used to thin the blood)
- phenytoin – **anti-epileptic** (used to treat epilepsy and seizures)
- nortriptyline, amitriptyline, imipramine, desipramine – **antidepressants** (used to treat depression)
- phenothiazines – **antipsychotics** (used to treat schizophrenia and psychosis)
- digoxin –used to treat **heart failure and atrial fibrillation**
- colchicine – used to treat **gout**
- metoprolol – used to **lower blood pressure and/or reduce heart rate**
- dextromethorphan – **cough medicine**
- atomoxetine – used to treat **attention deficit hyperactivity disorder (ADHD)**
- pravastatin – used to **lower cholesterol and prevent heart disease**

**Taking Cerdelga with food and drink**

Avoid consumption of grapefruit or grapefruit juice since it may increase the level of Cerdelga in your blood.

**Pregnancy, breast-feeding and fertility**

If you are pregnant, think that you may be pregnant or are planning to have a baby, tell your doctor who will discuss with you whether you can take this medicine during your pregnancy.

The active substance in this medicine has been shown to pass in trace amounts into breast milk in animals. Breast-feeding is not recommended during treatment with this medicine. Tell your doctor if you are breast-feeding.

There are no known effects on fertility at normal doses.

**Driving and using machines**

Cerdelga has negligible or no influence on the ability to drive and use machines.

**Cerdelga contains lactose**

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

**3. How to take Cerdelga**

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

If you are an intermediate metaboliser or extensive metaboliser:

Swallow one 84 mg capsule whole twice a day with water. It may be taken with or without food. Take one capsule in the morning and one capsule at night.

If you are a poor metaboliser:

Swallow one 84 mg capsule whole once a day with water. It may be taken with or without food. Take one capsule at the same time every day.

Do not open, crush, dissolve, or chew the capsule before swallowing it. If you cannot swallow the capsule whole, tell your doctor.

Continue taking Cerdelga every day for as long as your doctor tells you.

**How to pull the blister/wallet from the sleeve**

While pressing your thumb and finger together at one end of the sleeve (1) gently pull the blister/wallet out to open the sleeve (2).



**If you take more Cerdelga than you should**

If you take more capsules than you were told to, consult your doctor immediately. You may experience dizziness marked by loss of balance, slow heart rate, nausea, vomiting and light-headedness.

**If you forget to take Cerdelga**

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

**If you stop taking Cerdelga**

Do not stop taking Cerdelga without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

#### **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most of the side effects are mild and will generally disappear over time.

**Common** (may affect up to 1 in 10 people):

- Headache
- Dizziness
- Palpitations
- Heartburn (dyspepsia)
- Feeling sick (nausea)
- Diarrhoea
- Constipation
- Abdominal pain
- Stomach ache (upper abdominal pain)
- Acid reflux disease (gastrooesophageal reflux disease)
- Bloating (abdominal distension)
- Inflammation of the stomach (gastritis)
- Joint pain
- Tiredness (fatigue)

In clinical studies, a small number of patients fainted. All of these patients had risk factors for fainting. Please tell your doctor immediately if you are feeling faint or you have fainted.

### **Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Cerdelga**

Keep this medicine out of the sight and reach of children.

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.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Cerdelga contains**

- The active substance is eliglustat (as tartrate). Each capsule contains 84 mg eliglustat.
- The other ingredients are:
  - In the capsule: microcrystalline cellulose, lactose monohydrate (see section 2 under 'Cerdelga contains lactose'), hypromellose and glycerol dibehenate.
  - In the capsule shell: gelatin, potassium aluminium silicate (E555), titanium dioxide (E171), yellow iron oxide (E172) and indigotine (E132).
  - In the printing ink: shellac glaze, black iron oxide (E172), propylene glycol and ammonium hydroxide.

### **What Cerdelga looks like and contents of the pack**

Cerdelga capsules have a pearl blue-green opaque cap and a pearl white opaque body with "GZ02" printed in black on the capsule.

Pack sizes of 14 hard capsules in 1 blister wallet of 14 capsules, 56 hard capsules in 4 blister wallets of 14 capsules each or 196 hard capsules in 14 blister wallets of 14 capsules each

Not all packs may be marketed in your country.

**Marketing Authorisation Holder**

Genzyme Europe BV  
Gooimeer 10  
1411DD  
Naarden  
The Netherlands

**Manufacturer**

Genzyme Ireland Ltd  
IDA Industrial Park  
Old Kilmeaden Road  
Waterford  
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien/  
Luxembourg/Luxemburg**

Sanofi Belgium  
Tél/Tel: + 32 2 710 54 00

**България**

SANOFI-BULGARIA EOOD  
Тел: +359 2 9705300

**Česká republika**

sanofi-aventis, s.r.o.  
Tel: +420 233 086 111

**Danmark**

sanofi-aventis Denmark A/S  
Tlf: +45 45 16 70 00

**Deutschland**

Sanofi-Aventis Deutschland GmbH  
Tel.: 0800 04 36 996  
Tel. aus dem Ausland: +49 69 305 70 13

**Eesti**

sanofi-aventis Estonia OÜ  
Tel. +372 6 273 488

**Ελλάδα**

sanofi-aventis AEBE  
Τηλ: +30 210 900 1600

**España**

sanofi-aventis, S.A.  
Tel: +34 93 485 94 00

**France**

sanofi-aventis France  
Tél: 0 800 222 555  
Appel depuis l'étranger: +33 1 57 63 23 23

**Lietuva**

UAB „SANOFI-AVENTIS LIETUVA“  
Tel. +370 5 275 5224

**Magyarország**

SANOFI-AVENTIS Zrt.  
Tel: +36 1 505 0050

**Malta**

Sanofi Malta Ltd  
Tel: +356 21493022

**Nederland**

Genzyme Europe B.V.  
Tel: +31 35 699 1200

**Norge**

sanofi-aventis Norge AS  
Tlf: + 47 67 10 71 00

**Österreich**

sanofi-aventis GmbH  
Tel: + 43 1 80 185 - 0

**Polska**

sanofi-aventis Sp. z o.o.  
Tel.: +48 22 280 00 00

**Portugal**

Sanofi – Produtos Farmacêuticos, Lda.  
Tel: +351 21 35 89 400

**România**

Sanofi Romania SRL  
Tel: +40 (0) 21 317 31 36

**Hrvatska**

sanofi-aventis Croatia d.o.o.  
Tel: +385 1 600 34 00

**Ireland**

sanofi-aventis Ireland Ltd. T/A SANOFI  
Tel: +353 (0) 1 403 56 00

**Ísland**

Vistor hf.  
Sími: +354 535 7000

**Italia**

Sanofi S.p.A.  
Tel: +39 059 349 811

**Κύπρος**

sanofi-aventis Cyprus Ltd.  
Τηλ: +357 22 871600

**Latvija**

sanofi-aventis Latvia SIA  
Tel: +371 67 33 24 51

**Slovenija**

sanofi-aventis d.o.o.  
Tel: +386 1 560 4800

**Slovenská republika**

sanofi-aventis Pharma Slovakia s.r.o.  
Tel.: +421 2 33 100 100

**Suomi/Finland**

Sanofi Oy  
Puh/Tel: + 358 201 200 300

**Sverige**

Sanofi AB  
Tel: +46 (0)8 634 50 00

**United Kingdom**

Sanofi  
Tel: +44 (0) 845 372 7101

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**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments.