# 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 hard capsules

## 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

Hard capsule

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).

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

Special populations

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

*Patients with hepatic impairment*
In CYP2D6 extensive metabolisers (EMs) with severe (Child-Pugh class C) hepatic impairment, eliglustat is contraindicated (see sections 4.3 and 5.2).

In CYP2D6 extensive metabolisers (EMs) with moderate hepatic impairment (Child-Pugh class B), eliglustat is not recommended (see sections 4.4 and 5.2).

In CYP2D6 extensive metabolisers (EMs) with mild hepatic impairment (Child-Pugh class A), no dosage adjustment is required and the recommended dose is 84 mg eliglustat twice daily.

In CYP2D6 intermediate metabolisers (IMs) or poor metabolisers (PMs) with any degree of hepatic impairment, eliglustat is not recommended (see sections 4.4 and 5.2).

In CYP2D6 extensive metabolisers (EMs) with mild or moderate hepatic impairment taking a strong or moderate CYP2D6 inhibitor, Cerdelga is contraindicated (see sections 4.3 and 5.2).

In CYP2D6 extensive metabolisers (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 sections 4.4 and 5.2).

*Patients with renal impairment*
In CYP2D6 extensive metabolisers (EMs) with mild, moderate or severe renal impairment, no dosage adjustment is required and the recommended dose is 84 mg eliglustat twice daily (see sections 4.4 and 5.2).

In CYP2D6 EMs with end stage renal disease (ESRD), eliglustat is not recommended (see sections 4.4 and 5.2).

In CYP2D6 intermediate metabolisers (IMs) or poor metabolisers (PMs) with mild, moderate or severe renal impairment or ESRD, eliglustat is not recommended (see sections 4.4 and 5.2).

*Elderly*
There is limited experience in the treatment of elderly with eliglustat. Data indicates that no dosage adjustment is considered necessary (see sections 5.1 and 5.2).

*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.

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

## 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).

Due to significantly increased eliglustat plasma concentrations, Cerdelga is contraindicated in CYP2D6 extensive metabolisers (EMs) with severe hepatic impairment and in CYP2D6 extensive metabolisers (EMs) with mild or moderate hepatic impairment taking a strong or moderate CYP2D6 inhibitor (see sections 4.2 and 5.2).

## 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 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).

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

Use of eliglustat 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 eliglustat 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), long QT syndrome, and in combination with Class IA (e.g. quinidine) and Class III (e.g. amiodarone, sotalol) antiarrhythmic medicinal products.

Patients with hepatic impairment

Limited data are available in CYP2D6 extensive metabolisers (EMs) with moderate hepatic impairment. Use of eliglustat in these patients is not recommended (see sections 4.2. and 5.2).

Limited or no data are available in CYP2D6 intermediate metabolisers (IMs) or poor metabolisers (PMs) with any degree of hepatic impairment. Use of eliglustat in these patients is not recommended (see sections 4.2 and 5.2).

Concomitant use of eliglustat with CYP2D6 or CYP3A4 inhibitors in CYP2D6 extensive metabolisers (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 extensive metabolisers (EMs) with mild hepatic impairment taking a weak CYP2D6 inhibitor or strong, moderate or weak CYP3A inhibitor, a dose of 84 mg eliglustat mg once daily should be considered (see sections 4.2 and 5.2).

Patients with renal impairment

Limited or no data are available in CYP2D6 extensive metabolisers (EMs), intermediate metabolisers (IMs) or poor metabolisers (PMs) -with ESRD and in CYP2D6 intermediate metabolisers (IMs) or poor metabolisers (PMs) with mild, moderate, or severe renal impairment; use of eliglustat in these patients is not recommended (see sections 4.2 and 5.2).

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, total 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.

*In extensive metabolisers (EMs) with mild or moderate hepatic impairment:* see sections 4.2, 4.3 and 4.4.
*In extensive metabolisers (EMs) with severe hepatic impairment:* see sections 4.2 and 4.3.
*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 extensive metabolisers (EMs) with mild hepatic impairment:* see sections 4.2 and 4.4.

*In extensive metabolisers (EMs) with moderate or severe hepatic impairment:* see sections 4.2 and 4.3.

*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 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).

The most frequently reported adverse reaction with Cerdelga is dyspepsia, in approximately 6% of the clinical trial patients.

Tabulated list of adverse reactions

Adverse reactions are ranked by system organ class and frequency ([very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000)]). Adverse reactions from long term clinical trial data reported in at least 4 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*, dysgeusia |
| Cardiac disorders | Palpitations |
| Respiratory, thoracic and mediastinal disorders | Throat irritation |
| Gastrointestinal disorders | Dyspepsia, abdominal pain upper*, diarrhoea*, nausea, constipation, abdominal pain*, gastrooesophageal reflux disease, abdominal distension*, gastritis, dysphagia, vomiting*, dry mouth, flatulence |
| Skin and subcutaneous tissue disorders | Dry skin, urticaria* |
| Musculoskeletal and connective tissue disorders | Arthralgia, pain in extremity*, back pain* |
| 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.

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) [a] | Cerdelga (n=20) [a] | Difference (Cerdelga – Placebo) [95% CI] | p value[b] |
|---|---|---|---|---|
| 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
[a] 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 $10^9$/L, respectively.
[b] 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 ($mm^3$) 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 ($x10^9$/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] |
|---|---|---|
| Spleen Volume | | |
| Percentage of Patients with stable spleen volume*[a] | 100% | 95.8% |
| Percentage Change in Spleen Volume MN (%)* | -3.01 [-6.41, 0.40] | -6.17 [-9.54, -2.79] |
| Haemoglobin Level | | |
| Percentage of Patients with stable haemoglobin level[a] | 100% | 94.9% |
| Absolute Change in Haemoglobin Level (g/dL) | 0.038 [-0.16, 0.23] | -0.21 [-0.35, -0.07] |
| Liver Volume | | |
| Percentage of Patients with stable liver volume[a] | 93.6% | 96.0% |
| Percentage Change in Liver Volume MN (%) | 3.57 [0.57, 6.58] | 1.78 [-0.15, 3.71] |
| Platelet Count | | |
| Percentage of Patients with stable platelet count[a] | 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
[a] 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[a] Mean [95% CI] | Cerdelga[b] Mean [95% CI]) | Cerezyme /Cerdelga[a] Mean [95% CI] | Cerdelga[b] Mean [95% CI] | Cerezyme /Cerdelga[a] Mean [95% CI] | Cerdelga[b] 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 |
| **Spleen Volume** | | | | | | |
| 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] |
| **Haemoglobin Level** | | | | | | |
| 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] |
| **Liver Volume** | | | | | | |
| 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] |
| **Platelet Count** | | | | | | |
| 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] |
| **Composite Stability Endpoint** | | | | | | |
| 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.

Elderly

A limited number of patients aged 65 years (n=10) 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 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 6 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 in non-PMs and once daily in PMs, steady state was reached by 4 days, with an accumulation ratio of 3-fold or less.

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.

*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 1.2- and 1.2-fold higher in CYP2D6 extensive metabolisers (EMs) with mild hepatic impairment, and 2.8- and 5.2-fold higher in CYP2D6 extensive

metabolisers (EMs) with moderate hepatic impairment compared to healthy CYP2D6 extensive metabolisers (EMs).

After repeated 84 mg twice daily doses of Cerdelga, $C_{max}$ and $AUC_{0-12}$ are predicted to be 2.4- and 2.9-fold higher in CYP2D6 extensive metabolisers (EMs) with mild hepatic impairment and 6.4- and 8.9-fold higher in CYP2D6 extensive metabolisers (EMs) with moderate hepatic impairment compared to healthy CYP2D6 extensive metabolisers (EMs).

After repeated 84 mg once daily doses of Cerdelga, $C_{max}$ and $AUC_{0-24}$ are predicted to be 3.1- and 3.2 -fold higher in CYP2D6 extensive metabolisers (EMs) with moderate hepatic impairment compared to healthy CYP2D6 extensive metabolisers (EMs ) receiving Cerdelga 84 mg twice daily (see sections 4.2 and 4.4).
Steady state PK exposure could not be predicted in CYP2D6 intermediate metabolisers (IMs) and poor metabolisers (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 sections 4.2, 4.3 and 4.4).

*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 extensive metabolisers (EMs) with severe renal impairment and healthy CYP2D6 extensive metabolisers (EMs).

Limited or no data were available in patients with ESRD and in CYP2D6 intermediate metabolisers (IMs) or poor metabolisers(PMs) with severe renal impairment (see sections 4.2 and 4.4).

## 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 ≥ 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 anaesthesised 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
Black iron oxide (E172)
Propylene glycol
Ammonia solution, concentrated

### 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., Paasheuvelweg 25, 1105 BP Amsterdam, 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
Date of latest renewal: 16 December 2019

## 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 (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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 marketing authorisation holder (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.

- **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).

- 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 (IMs) or extensive metabolisers (EMs) 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 (PMs) 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. Use of a moderate CYP3A inhibitor with eliglustat is not recommended in PMs.
- A dose of eliglustat 84 mg once daily should be considered when a strong CYP2D6 inhibitor is used concomitantly in intermediate metabolisers (IMs) and extensive metabolisers (EMs).
- Caution should be used with moderate CYP2D6 inhibitors in intermediate metabolisers (IMs) and extensive metabolisers (EMs). Caution should be used with strong or moderate CYP3A inhibitors in intermediate metabolisers (IMs) and extensive metabolisers (EMs). Caution should be used with weak CYP3A inhibitors in poor metabolisers (PMs).
- In CYP2D6 extensive metabolisers (EMs) with severe hepatic impairment, Cerdelga is contraindicated. In CYP2D6 extensive metabolisers (EMs) with mild or moderate hepatic impairment taking a strong or moderate CYP2D6 inhibitor, Cerdelga is contraindicated.
- In CYP2D6 extensive metabolisers (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.
- In CYP2D6 intermediate metabolisers (IMs) or poor metabolisers (PMs) with any degree of hepatic impairment, Cerdelga 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. In addition, patient's hepatic or renal status may have an impact on the metabolism of eliglustat.

- Using eliglustat together with such products or in patients with hepatic or renal impairment 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.
Paasheuvelweg 25
1105 BP Amsterdam
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

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Cerdelga

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**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.

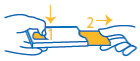
## 4. PHARMACEUTICAL FORM AND CONTENTS

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.
Paasheuvelweg 25
1105 BP Amsterdam
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 hard capsules**
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

Cerdelga contains the active substance eliglustat and is 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 are an intermediate or extensive metaboliser 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 are a poor metaboliser and use medicines known as strong CYP3A inhibitors (for example itraconazole). Medicines of this type will interfere with your body's abilty 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 are an extensive metaboliser and you have severely reduced liver function.
- If you are an extensive metaboliser and you have mildly or moderately reduced liver function while taking a strong or moderate CYP2D6 inhibitor.

**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, inluding 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.
- are an extensive metaboliser and you have moderately reduced liver function.
- are an intermediate or poor metaboliser and you have any level of reduced liver function.
- are an intermediate or poor metaboliser and you have reduced kidney function.
- are an end stage renal disease (ESRD) patient.

**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)
- nortryptyline, 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.

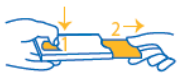
If you are an intermediate metaboliser or extensive metaboliser:
Swallow one 84 mg capsule whole twice a day with water. It may be taken with or without food. Take one capsule in the morning and one capsule at night.

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.

**Common** (may affect up to 1 in 10 people):
- Headache
- Dizziness
- Change in taste (dysgeusia)
- Palpitations
- Throat irritation
- 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)

- Difficulty swallowing (dysphagia)
- Vomiting
- Dry mouth
- Gas (flatulence)
- Dry skin
- Hives (urticaria)
- Joint pain (arthalagia)
- Pain in arms, legs or back
- Tiredness (fatigue)

**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, black iron oxide (E172), propylene glycol and ammonia solution, concentrated.

**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, 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 B.V.
Paasheuvelweg 25
1105 BP Amsterdam
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**
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

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

**Danmark**
Sanofi 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**
Swixx Biopharma OÜ
Tel: +372 640 10 30

**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

**Hrvatska**
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

**Lietuva**
Swixx Biopharma UAB
Tel: +370 5 236 91 40

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

**Malta**
Sanofi S.r.l.
Tel: +39 02 39394275

**Nederland**
Genzyme Europe B.V.
Tel: +31 20 245 4000

**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

**Slovenija**
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 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.r.l.
Tel: 800 536 389

**Κύπρος**
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

**Latvija**
Swixx Biopharma SIA
Tel: +371 6 616 47 50

**Slovenská republika**
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

**Suomi/Finland**
Sanofi Oy
Puh/Tel: + 358 201 200 300

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

**United Kingdom (Northern Ireland)**
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

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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.