1. NAME OF THE MEDICINAL PRODUCT

Cerdelga

Patient Safety Information Card

The marketing of Cerdelga is subject to a risk management plan (RMP) including a 'Patient safety information card'. The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment. Please explain the patient the need to review the card before starting treatment.

Prescriber Guide

This product is marked with prescriber guide providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

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_{max} 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. amlopidine, 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 commonly reported adverse reaction with Cerdelga is diarrhoea, in approximately 6% of the patients. Less than 2% of patients receiving Cerdelga permanently discontinued treatment due to any adverse reaction.

The most frequently reported serious adverse reaction in clinical studies was syncope (0.76%). 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 pooled results from the primary analysis periods of two pivotal studies and one 4-year, long term study, with a total of 152 patients who received eliglustat for a median duration of 51.9 weeks (range 0.1 to 210.9 weeks) and between the ages of 16 - 69 years.

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)]). 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

Nervous system disorders	
Common	Headache*
Gastrointestinal disorders	
Common	Nausea, diarrhoea*, abdominal pain*, flatulence
Musculoskeletal and connective tissue disorders	
Common	Arthralgia
General disorders and administration site conditions	
Common	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 authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

(http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il).

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

During an open-label extension period, patients who continued to receive Cerdelga (n=18) showed further improvements (change from baseline) in haemoglobin level (1.02 g/dL), platelet count (58.16%) and spleen and liver volumes (-44.61% and -11.18% respectively) after 18 months of treatment. All patients had ≥ 20% reduction in spleen volume after 18 months, and the vast majority (16/18) of patients achieved > 30% reduction in spleen volume.

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.

Cerdelga showed sustained improvements in organ volume and haematological parameters over the 4 year treatment period (see Table 3).

Table 3: Change from baseline to year 4 in study 304

	N	Baseline Value (Mean)	Change from Baseline (Mean)	95% Confidence Interval	p-value[a]
Spleen Volume (MN)	18	17.32	-62.5%	(-68.3, -56.7)	<0.0001
Haemoglobin Level (g/dL)	19	11.30	2.27	(1.57, 2.97)	<0.0001
Liver Volume (MN)	18	1.70	-28.0%	(-34.9, -21.2)	<0.0001
Platelet Count (x10^9/L)	19	68.68	95.0%	(50.7, 139.4)	0.0003

MN = Multiples of Normal

[a] Paired t-test

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.
[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.

During an open-label extension period the percentage of patients meeting the composite stability endpoint was maintained at 87.4% after 24 months of treatment with Cerdelga. Individual disease parameters of spleen volume, liver volume, haemoglobin levels and platelet count remained stable through 24 months.

Clinical experience in CYP2D6 poor metabolisers (PMs) and ultra-rapid metabolisers (URMs)
There is limited experience with Cerdelga treatment of patients who are PMs or URMs. In the primary analysis periods of the three clinical studies, a total of 5 PMs and 5 URMs were treated with Cerdelga. All PMs received 42 mg eliglustat twice daily, and four of these (80%) had an adequate clinical response. The majority of URMs (80%) received a dose escalation to 127 mg eliglustat twice daily, all of which had adequate clinical responses. The one URM who received 84 mg twice daily did not have an adequate response.

The predicted exposures with 84 mg eliglustat once daily in patients who are PMs are expected to be similar to exposures observed with 84 mg eliglustat twice daily in CYP2D6 intermediate metabolisers

(IMs). Patients who are URMs may not achieve adequate concentrations to achieve a therapeutic effect. No dosing recommendation for URMs can be given.

Effects on skeletal pathology
In Study 02507, the total Bone Marrow Burden (BMB) score as assessed by MRI in lumbar spine and femur in Cerdelga-treated patients decreased by a mean of 1.1 points after 9 months (n=20) and 2.15 points after 18 months (n=18). The percentage of Cerdelga-treated patients with a significant reduction of at least 2 points in the total BMB score increased from 26% (n=5) after 9 months to 44% (n=8) after 18 months.
After 18 months of Cerdelga treatment, the mean (SD) lumbar spine bone mineral density (BMD) T-score increased from -1.06 (0.82) (n=17), to -0.91 (0.88) (n=15).

Results of study 304 indicate that skeletal improvements are maintained or continue to improve during at least 4 years of treatment with Cerdelga.

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.

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Storage

Below 30 ◦C

6.5 Nature and contents of container

PETG/COC.PETG/PCTFE-aluminium blister

Each blister wallets contains 14 hard capsules.
Each pack contains 14 or 56 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. MANUFACTURER

Genzyme Ireland, Ltd,
Waterford, Ireland.

8. MARKETING AUTHORISATION HOLDER

Sanofi-aventis Israel Ltd.

9. MARKETING AUTHORISATION NUMBER

157-56-34703

This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved in December 2016