EMA/743948/2014

Summary of the risk management plan (RMP) for Cerdelga (eliglustat)

This is a summary of the risk management plan (RMP) for Cerdelga, which details the measures to be taken in order to ensure that Cerdelga is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Cerdelga, which can be found on Cerdelga's EPAR page.

Overview of disease epidemiology

Cerdelga is a medicine used to treat type-1 Gaucher disease (GD1), a rare inherited disorder in which people do not have enough of an enzyme called glucocerebrosidase (also known as acid beta-glucosidase). This enzyme normally breaks down a fat called glucosylceramide (or glucocerebroside), and without it, the fat builds up in the body, typically in the liver, spleen and bones, causing a number of signs and symptoms such as anaemia (low red blood cell counts), tiredness, easy bruising and a tendency to bleed, an enlarged spleen and liver, and bone pain and breaks.

Cerdelga is used in adults who have type-1 Gaucher disease, the type that usually affects the liver, spleen and bones. Between 1 to 3 out of 100,000 persons in the European Union have type-1 Gaucher disease.

Summary of treatment benefits

Cerdelga contains the active substance eliglustat and is available as capsules. It works by slowing down the production of glucosylceramide, preventing its build-up in the organs.

Cerdelga is for use only in adults whose body breaks down this medicine at normal or slow speed. Before starting treatment with Cerdelga, a test should be carried out to find out how rapidly the medicine is broken down in the patient's bodies.

Cerdelga has been shown to be effective in treating Gaucher disease in two main studies.

The first study involved 40 previously untreated patients with type-1 Gaucher disease, and it looked mainly at the reduction in the size of patients' spleens. Patients who were given eliglustat showed an average reduction of 28% in spleen size, compared with a 2% increase in those given placebo (a dummy treatment) after 9 months of treatment. Patients who received Cerdelga also showed an improvement of other signs of the disease such as a reduction in liver size and increased levels of haemoglobin (the protein found in red blood cells that carries oxygen around the body).

Cerdelga was also shown to be effective in another study involving 160 patients with type-1 Gaucher disease, who had been previously treated with a therapy to replace the missing enzyme and whose disease symptoms were under control. Some of the patients were treated with Cerdelga, while others were treated with enzyme replacement therapy. This study found that, after treatment for a year, the

disease remained stable in 85% of patients treated with Cerdelga compared with 94% of patients who continued with the enzyme replacement therapy.

Unknowns relating to treatment benefits

There is limited information on the long-term treatment effects of Cerdelga in adult patients with type-1 Gaucher disease.

Summary of safety concerns

Important identified risks

There are no important identified risks.

Important potential risks

Risk	What is known
Interactions with other medicines that may reduce the breakdown of Cerdelga, or with grapefruit products (use with CYP2D6 and/or CYP3A inhibitors)	Certain medicines and grapefruit products may increase the level of Cerdelga in the blood ('CYP2D6 and/or CYP3A inhibitors'). Cerdelga must not be used with strong or moderate CYP2D6 or CYP3A inhibitors. Consumption of grapefruit or its juice should be avoided. • Examples of medicines which may have a strong effect on Cerdelga are: paroxetine and fluoxetine (used to treat depression), quinidine (used to treat irregular heartbeat), and itraconazole and clarithromycin (used to treat infections). • Examples of medicines which may have a less strong (moderate) effect on Cerdelga are: duloxetine (used in depression and anxiety disorders) and terbinafine, fluconazole and erythromycin (used to treat infections).
Interactions with other medicines that may speed up the breakdown of Cerdelga (use with strong CYP3A inducers)	There are also certain medicines that may decrease the level of Cerdelga in the blood and thereby reduce the effectiveness of Cerdelga ('strong CYP3A inducers'). Therefore it is not recommended to give Cerdelga in combination with these medicines.
Interactions with other medicines for which Cerdelga may slow down their breakdown (use with P-gp or CYP2D6 substrates)	Cerdelga may increase the level of some medicines in the blood ('P-gp substrates and CYP2D6 substrates'). The dosage of these medicines may have to be decreased.
Use in patients whose body breaks down Cerdelga at unknown speed	There are differences among people in the speed that their body breaks down Cerdelga, which depends on the functioning of a specific enzyme in the liver. As a result, the level of Cerdelga in the blood may vary. A test should be carried out before starting treatment with Cerdelga to find out if the patient's body breaks down Cerdelga at the required normal or slow

Risk	What is known
	speed.
Irregular or abnormal heart beat and conditions that affect the heart rhythm (cardiac conduction disorders and arrhythmias)	A small number of patients treated with Cerdelga in the clinical studies experienced mild events of irregular or abnormal heart beat. In most cases, these were considered not related to treatment with Cerdelga. There is a risk of irregular or abnormal heart beat and changes in the electrical activity of the heart (which may affect the heart rhythm) when levels of Cerdelga in the blood are very high. Situations which may lead to very high levels of Cerdelga in the blood should be avoided.
Fainting (vasovagal syncope)	In clinical studies, a small number of female patients experienced fainting while taking Cerdelga. In those cases, medical reasons other than taking Cerdelga could explain the fainting. All patients were able to continue treatment with Cerdelga.
Unapproved (off label) use in Gaucher disease type-2 and -3	Cerdelga is not intended for use other than in adult patients with type-1 Gaucher disease. Use in disease subtypes other than type-1 has not been sufficiently investigated.
A disorder of the nerves which can cause weakness, tingling or numbness (peripheral neuropathy)	A small number of patients treated with Cerdelga in clinical trials experienced numbness and/or tingling in their hands and/or feet. In those cases medical reasons other than taking Cerdelga could explain these findings. The events of numbness and/or tingling were mild, non-serious, and the patients were able to continue taking Cerdelga.

Missing information

Risk	What is known
Use in patients with heart disease or heart rhythm problems (use in patients with a history of current cardiac ischaemia or heart failure, clinically significant arrhythmias or conduction findings)	Patients with heart disease or heart rhythm problems were excluded from the clinical studies with Cerdelga, since there is a potential risk of an effect on the electrical activity of the heart when levels of Cerdelga in the blood are very high. Therefore, the use of Cerdelga in patients with heart disease or heart rhythm problems should be avoided.
Use in patients with liver problems (hepatic impairment)	Cerdelga is broken down in the liver. Patients with liver problems were excluded from the studies with Cerdelga. Therefore, there are no data available on the use of Cerdelga in these patients.
Use in children	The studies conducted in patients with type-1 Gaucher disease to date included only a very small number of children. No conclusions can be drawn.
Use in patients who are pregnant or breastfeeding	Animal studies showed no harmful effect in the offspring, no passing of Cerdelga into milk and no transfer of Cerdelga to the unborn animal. However, as pregnant and breastfeeding women were excluded from the clinical studies with Cerdelga no conclusions can be drawn. Thus, it is

Risk	What is known
	recommended to avoid the use of Cerdelga during pregnancy. It is unknown whether Cerdelga is excreted in human milk. Breastfeeding is not recommended during treatment with Cerdelga.
Safety with long-term use	The current safety profile of Cerdelga has been established based on data collected in patients treated on average for up to 3 years. No information is available on treatments longer than 3 years.
Use in patients whose body breaks down Cerdelga at faster speed (use in patients who are CYP2D6 ultra-rapid metabolisers or 'URM')	It is possible that Cerdelga is not effective enough in URM patients treated with 100 mg twice a day; however, no conclusions can be made based on the limited available data. Cerdelga should not be used in URM patients.
Use in patients with kidney problems (renal impairment)	Patients with kidney problems were excluded from the clinical studies with Cerdelga. Therefore, there are no data available on the use of Cerdelga in these patients.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Cerdelga can be found on Cerdelga's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use ('additional risk minimisation measures'). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published on Cerdelga's EPAR page; how they are implemented in each country however, will depend upon agreement between the marketing authorisation holder and the national authorities.

These additional risk minimisation measures are for the following risks:

Interaction with other medicines that may increase or decrease the level of Cerdelga in the blood, with grapefruit products, and with medicines for which Cerdelga may slow down their breakdown (use with CYP2D6 and/or CYP3A inhibitors- Use with strong CYP3A inducers – Use with P-gp or CYP2D6 substrates)

Risk minimisation measure: Healthcare professional and patient educational material
Objective and rationale: • To prevent situations that may cause large increases in Cerdelga levels in the blood to very high levels and to prevent situations where Cerdelga may increase the levels of other medicines in the body. Educating health care professionals and patients on what medicines, over-the-counter medicines or herbal products they cannot prescribe or should not be used

together with Cerdelga, and to inform patients not to consume grapefruit products.
Description: • Healthcare professional educational material: The guide for the prescriber includes a checklist of actions to be taken before starting treatment with Cerdelga, including checking and warning for medicines that may alter the effect of Cerdelga or that may be affected by Cerdelga. • Patient educational material: Patient alert card to remind the patient to consult their doctor before starting any new prescription medicine, over-the-counter medicine or herbal product. The patient alert card informs about current treatment with Cerdelga and medicines that should not be prescribed or used together with Cerdelga.

Use in patients whose body breaks down Cerdelga at unknown speed (use of eliglustat in patients for whom the ability to break down the medicine is unknown or for whom no test has been done)

Risk minimisation measure: Healthcare professional educational material
Objective and rationale: To remind healthcare professionals to determine for each patient at what speed their body breaks down Cerdelga. Patients for whom the ability to break down the medicine is unknown or for whom no test has been done should not use Cerdelga.
Description: The guide for the prescriber includes a checklist of actions to be taken before starting treatment with Cerdelga, including the need to determine the speed at which the patient's body breaks down Cerdelga.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Prospective ICGG safety sub-registry	To characterise the long-term safety profile of Cerdelga in real-world clinical practice. To describe the patients' characteristics and utilisation patterns.	• Safety in long-term treatment use. • Use in patients for whom the ability to break down the medicine is unknown or for whom no test has been done. • Off-label use in Gaucher disease type 2 and 3. • Use of eliglustat in patients who are ultra-rapid metabolisers.	Planned.	Concept protocol will be submitted within 3 months after approval. Milestones will be reported in PSURs. Re-evaluation at 5 year after first Cerdelga patient has been entered.
Paediatric study in patients with	To evaluate pharmacokinetics (how	Use in children	Planned	Planned final report: Q4 2021.

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Gaucher disease type 1 and 3	the medicine is broken down in the body), safety, and efficacy of Cerdelga in children with Gaucher disease type-1 and -3.			
Pharmacokinetics of oral single-dose eliglustat in subjects with hepatic dysfunction	To evaluate the pharmacokinetics of eliglustat in subjects with liver impairment	Use in patients with liver impairment.	Planned	Planned final report: Q3 2017.
Pharmacokinetics of oral single-dose eliglustat in subjects with renal impairment	To evaluate eliglustat pharmacokinetics in subjects with kidney impairment after administration of eliglustat.	Use in patients with kidney impairment.	Planned	Planned final report: Q3 2017.
Drug utilisation study of eliglustat in Europe using electronic healthcare records	To assess compliance/adherence to the labelling with regard to interactions with other medicines.	Drug-drug interaction.	Planned	Pilot study report: Q3 2014. Annual reports starting one year after launch in EU. Final report 4 years after launch in EU.
Drug utilisation study of eliglustat in the US population using the Marketscan® database	To assess compliance/adherence to the labelling with regard to interactions with other medicines. To assess compliance/adherence to the labelling with regard to assessment of whether patients are slow or normal metabolisers.	• Drug-drug interaction. • Use in patients for whom the ability to break down the medicine is unknown or for whom no test has been done. • Use in patients who are CYP2D6 ultra-rapid metabolisers.	Planned	Annual reports starting one year after launch in US. Final report 4 years after launch in US.
Phase 2 open label, uncontrolled study in patients with GD1 who	To determine the long-term efficacy, safety, and pharmacokinetic effects of Cerdelga.	Long-term safety and efficacy.	Ongoing	August 2016

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
were untreated or had not been treated in preceding 12 months (GZGD00304)				
Phase 3, randomised, double-blind, placebo-controlled study in patients with GD1 who were untreated or had not been treated in preceding 9 months (GZGD02507)	To determine the long-term efficacy, safety, and pharmacokinetics of Cerdelga in patients with type-1 Gaucher disease.	Long-term safety and efficacy.	Ongoing	July 2016
Phase 3, randomised, open-label, active comparator study in patients with GD1 who achieved therapeutic goals with long-term ERT (GZGD02607)	To study the long-term efficacy, safety and pharmacokinetics of Cerdelga in patients with type-1 Gaucher disease who have reached therapeutic goals with enzyme replacement therapy (ERT).	Long-term safety and efficacy.	Ongoing	November 2015
Phase 3 randomised, double-blind, study to evaluate QD vs BID dosing in patients with GD1 who demonstrate clinical stability on BID dosing (GZGD03109)	To evaluate the efficacy and safety of once daily (QD) versus twice daily (BID) dosing of Cerdelga in patients with type-1 Gaucher disease who have demonstrated clinical stability on BID dosing of Cerdelga.	Efficacy of QD vs BID dosing.	Ongoing	March 2016
Aggregate report of adverse events from the studies	To assess long-term safety.	Safety with long-term use.	Planned	Statistical Analysis Plan: Q4 2015. Submission of

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
GZGD00304, GZGD02507, GZGD02607, GZGD03109				final report: Q4 2016.
Collect and report long-term efficacy data from the International Collaborative Gaucher Group (ICGG) Gaucher Registry	To determine the long-term efficacy data on eliglustat-treated patients.	Long-term efficacy.	Planned	Registry report will be submitted bi-annually starting in Q4 2016, last report in Q4 2020.

Studies which are a condition of the marketing authorisation

None.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 12-2014.