Summary of the Risk Management Plan (RMP) for Cerdelga®

Cerdelga® (eliglustat)

Marketing Authorisation Holder : Sanofi-Aventis (Suisse) SA
EU-RMP version 8.3
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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Cerdelga® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation/Information sur le medicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisation.

Please note that the reference document which is valid and relevant for the effective and safe use of Cerdelga® in Switzerland is the "Arzneimittelinformation/ Information sur le medicament" (see www.swissmedicinfo.ch) approved and authorised by Swissmedic. Sanofi-Aventis (Suisse) SA is fully responsible for the accuracy and correctness of the content of this published summary RMP of Cerdelga®.

I. THE MEDICINE AND WHAT IT IS USED FOR

CERDELGA is authorized for the long-term treatment of adult patients with Gaucher disease type 1 (GD1). The target population is patients who are Cytochrome P4502D6 poor metabolizers (PMs), intermediate metabolizers (IMs) or extensive metabolizers (EMs) (see SmPC for the full indication). It contains eliglustat as the active substance, and it is given by oral route of administration. CERDELGA is proposed for paediatric patients with GD1 who are 6 years old and older with a minimum body weight of 15 kg, who are stable on enzyme replacement therapy (ERT), and who are CYP2D6 PMs, IMs or EMs. (see EU-SmPC for the full indication).

Further information about the evaluation of CERDELGA's benefits can be found in CERDELGA's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/documents/overview/cerdelga-epar-medicine-overview_en.pdf

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of CERDELGA, together with measures to minimize such risks and the proposed studies for learning more about CERDELGA's risks, are outlined in the next sections.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of CERDELGA, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, outlined in the next sections.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of CERDELGA is not yet available, it is listed under "missing information" outlined in the next section.

II.A List of important risks and missing information

Important risks of CERDELGA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of CERDELGA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

Table 40 - List of important risks and missing information

Important identified risk	None
Important potential risks	Drug-drug interactions - Use with CYP2D6 and/or CYP3A inhibitors - Use with strong CYP3A inducers - Use with P-glycoprotein (P-gp) or CYP2D6 substrates Use of eliglustat in patients who are CYP2D6 indeterminate metabolizers or non-genotyped patients Cardiac conduction disorders and arrhythmias
Missing information	Use in patients with a history of or current cardiac ischemia or heart failure, clinically significant arrhythmias or conduction findings Use during pregnancy and lactation Safety in long-term treatment use Use in patients who are CYP2D6 ultra-rapid metabolizers (URMs)

CYP: Cytochrome P450; P-gp: P-Glycoprotein; URM: Ultra-Rapid Metabolizer.

II.B Summary of important risks

Table 41 - Important risks with corresponding risk minimization activities and additional pharmacovigilance activities: Drug-drug interactions - Use with CYP2D6 and/or CYP3A inhibitors - Use with strong CYP3A inducers - Use with P-glycoprotein (P-gp) or CYP2D6 substrates

Important potential risk: Drug-drug interactions - Use with CYP2D6 and/or CYP3A inhibitors - Use with strong CYP3A inducers - Use with P-gp or CYP2D6 substrates	
Evidence for linking the risk to the medicine	Drug-drug interaction studies were conducted in healthy volunteers to investigate potential interactions between eliglustat and other drugs that are CYP2D6 or CYP3A inhibitors, CYP3A inducers, or P-gp or CYP2D6 substrates. Additionally, PBPK simulations were performed to evaluate Genz-99067 exposure under various scenarios of co-administration with interacting drug. **For strong/moderate/weak CYP2D6 inhibitors**: GZGD02007; SIM0106; SIM0319 **For strong/moderate/weak CYP3A inhibitors:** GZGD01807; SIM0106; SIM0170 and SIM0183, SIM0319 **Use of strong/moderate CYP2D6 inhibitor and strong/moderate CYP3A inhibitor:** SIM0105; SIM0106 **For Strong CYP3A inducer:** GZGD02407 **For P-gp inhibition:** GZGD03610 **For CYP2D6 inhibition:** GZGD04112; SIM0105
Risk factors and risk groups.	• Patients with hepatic impairment. • Consumption of grapefruit products (CYP3A inhibitors).
Risk minimization measures	**Routine risk minimization measures:** • Labeled in sections 4.2, 4.3, 4.4, 4.5 and 5.2 of SmPC. • Labeled in sections 2 and 3 of PIL. **Additional risk minimization measures:** • Guide for Prescriber. • Patient Card.
Additional pharmacovigilance activities	Drug utilization study in Europe (ELIGLC06913).

CYP: Cytochrome P450; PBPK: Physiologically Based Pharmacokinetic; P-gp: P-Glycoprotein; SmPC: Summary of Product Characteristics

Table 42 - Important risks with corresponding risk minimization activities and additional Pharmacovigilance activities: Use of eliglustat in patients who are CYP2D6 indeterminate metabolizers or non-genotyped patients

Important potential risk: Use of eliglustat in patients who are CYP2D6 indeterminate metabolizers or non-genotyped patients	
Evidence for linking the risk to the medicine	POH0373, SIM0105, SIM0183, and clinical studies.
Risk factors and risk groups.	Not applicable
Risk minimization measures	**Routine risk minimization measures:** • Labeled in sections 4.1, 4.2 and 5.2 of SmPC.
Risk minimization measures	**Routine risk minimization measures:** • Labeled in sections 4.1, 4.2 and 5.2 of SmPC. • Labeled in sections 2 and 3 of PIL. • Before initiation of treatment with CERDELGA, patients should be genotyped for CYP2D6 to determine the CYP2D6 metabolizer status. **Additional risk minimization measures:** Guide for Prescriber
Additional pharmacovigilance activities	Prospective ICGG safety sub-registry (OBS14099).

Table 43 - Important risks with corresponding risk minimization activities: Cardiac conduction disorders and arrhythmias

Important potential risk: Cardiac conduction disorders and arrhythmias	
Evidence for linking the risk to the medicine	ISS; ISS ECG Report; GZGD00304, GZGD02507; GZGD02607; GZGD03109; Aggregate AE Report.
Risk factors and risk groups.	Cardiac conduction disorders Patients with a prior history of conduction disease are more likely to experience blocks. There is an increased risk of first-degree block with increased age as well as some medical conditions (eg, ischemic heart disease, congenital heart disease, drugs, alcohol use, thyroid disease). Mobitz 1 second degree AV block can occur in normal subjects, athletes, older adults, and in patients with certain heart diseases or who are taking drugs that block the AV node (eg, digoxin, beta blockers, calcium channel blockers). Ventricular arrhythmia Patients with compromised heart function such as cardiomyopathy, heart failure and ischemia are at increased risk for ventricular arrhythmia. Coronary heart disease was identified as the underlying cause of 62% of sudden cardiac deaths. Higher rates of sudden cardiac death were associated with increased age and male gender. (69) Patients with congenital long QT syndrome are at greater risk for a long QTc interval. The use of medications that are known torsadogens or potential torsadogens are also known to increase the QTc interval, which may put a patient at increased risk of Torsade de Pointes. The effect of taking multiple drugs may be additive. Use of concomitant CYP2D6 and CYP3A inhibitors Extensive metabolizers and IMs using concomitant strong or moderate CYP2D6 inhibitors together with strong or moderate CYP3A inhibitors, and PMs using a strong CYP3A inhibitor are at increased risk to achieve substantially elevated eliglustat exposure which could potentially lead to increases in ECG intervals. Hepatic impairment Since metabolism is the predominant route of elimination, CYP2D6 IM and PM patients with any degree of HI and CYP2D6 EM patients with moderate and severe HI, as well as CYP2D6 EM patients with mild HI using a strong or moderate CYP2D6 inhibitor, are at increased risk to achieve substantially elevated eliglustat exposure which could potentially lead to increases in ECG intervals.
Risk minimization measures	**Routine risk minimization measures:**
	• Labeled in sections 4.3, 4.4 and 4.5 of SmPC. • Labeled in section 2 of PIL. **Additional risk minimization measures:** None

AE: Adverse Event; AV: Atrioventricular; CYP: Cytochrome P450; ECG: Electrocardiogram; EM: Extensive Metabolizer; HI: Hepatic Impairment; IM: Intermediate Metabolizer; ISS: Integrated Safety Summary; PM: Poor Metabolizer; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 44 - Missing information with corresponding risk minimization activities: Use in patients with a history of or current cardiac ischemia or heart failure, clinically significant arrhythmias, or conduction findings

Missing Information: Use in patients with a history of or current cardiac ischemia or heart failure, clinically significant arrhythmias or conduction findings	
Risk minimization measures	**Routine risk minimization measures:** • Labeled in section 4.4 of SmPC. • Labeled in section 2 of PIL. **Additional risk minimization measures:** None

PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 45 – Missing information with corresponding risk minimization activities: Use during pregnancy and lactation

Missing information: Use during pregnancy and lactation	
Risk minimization measures	**Routine risk minimization measures:** • Labeled in section 4.6 of SmPC. • Labeled in section 2 of PIL. **Additional risk minimization measures:** None

PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 46 – Missing information with corresponding additional pharmacovigilance activities: Safety in long-term treatment use

Missing information: Safety in long-term treatment use	
Risk minimization measures	**Routine risk minimization measures:** None **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Prospective ICGG safety sub-registry (OBS14099).

ICGG: International Collaborative Gaucher Group.

Table 47 - Missing information with corresponding risk minimization activities additional pharmacovigilance activities: Use in patients who are CYP2D6 ultra-rapid metabolizers (URMs)

Missing information: Use in patients who are CYP2D6 ultra-rapid metabolizers (URMs)	
Risk minimization measures	**Routine risk minimization measures:** • Labeled in sections 4.2 and 4.4 of SmPC. • Labeled in section 2 of PIL. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Prospective ICGG safety sub registry (OBS14099).

ICGG: International Collaborative Gaucher Group; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics; URM: Ultra-Rapid Metabolizer.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

The following studies are conditions of the marketing authorization:

Table 44 - Studies which are conditions of the marketing

authorization Prospective ICGG safety sub-registry (OBS14099)
Purpose of the study: A prospective ICGG safety sub registry to characterize the long-term safety profile of eliglustat. To describe the patient's characteristics and utilization patterns.

ICGG: International Collaborative Gaucher Group.

II.C.2 Other studies in post-authorization development plan

Table 45 - Other studies in post-authorization development plan

Drug utilization study of eliglustat in Europe using electronic healthcare records (ELIGLC06913)
Purpose of the study: To assess compliance/adherence to the labeling with regard to drug-drug interactions.

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