Cerdelga

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
X/0036/G	This was an application for a group of variations. Extension application to introduce a new strength (21 mg capsule, hard) grouped with an extension of indication (C.I.6.a) to include treatment of paediatric patients with GD1 who are 6 years and older with a	17/10/2024	06/12/2024	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion 'Cerdelga-H-C-3724-X-36-G'.

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	minimum body weight of 15 kg, who are stable on enzyme replacement therapy (ERT), and who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs), based on interim results from study EFC13738 (Open label, two cohort (with and without imiglucerase), multicenter study to evaluate pharmacokinetics, safety, and efficacy of eliglustat in paediatric patients with Gaucher disease type 1 and type 3). The above indication is approved for the new strength (21 mg) and the existing strength (84 mg) and as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took this opportunity to introduce editorial changes and to align the product information with the latest version of the QRD guideline. The RMP version 8.3 was agreed during the procedure. Annex I_2.(c) Change or addition of a new strength/potency C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
N/0037	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/07/2024	06/12/2024	PL	
IB/0035/G	This was an application for a group of variations. B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the	29/11/2023	29/05/2024	Annex II and PL	

	finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.e.7.z. - Change in supplier of packaging components or devices (when mentioned in the dossier) - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site				

	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
IB/0033	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	18/07/2023	n/a		
IAIN/0034	A.1 - Administrative change - Change in the name and/or address of the MAH	30/06/2023	29/05/2024	SmPC, Labelling and PL	
II/0032	Update of section 4.8 of the SmPC in order to add cough to the list of adverse drug reactions (ADRs) with frequency Common based on the cumulative review of clinical trial data, MAH global pharmacovigilance database and literature search. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	29/06/2023	29/05/2024	SmPC and PL	n/a
PSUSA/10351 /202208	Periodic Safety Update EU Single assessment - eliglustat	14/04/2023	n/a		PRAC Recommendation - maintenance
IB/0030/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a	02/03/2023	n/a		

	starting material/reagent/intermediate for AS - Other variation				
IA/0031/G	This was an application for a group of variations. B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or	21/12/2022	n/a		

	deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer				
IB/0028	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	20/01/2022	n/a		
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/11/2021	29/05/2024	PL	
PSUSA/10351 /202008	Periodic Safety Update EU Single assessment - eliglustat	11/03/2021	n/a		PRAC Recommendation - maintenance
N/0025	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/10/2020	29/05/2024	PL	
PSUSA/10351 /201908	Periodic Safety Update EU Single assessment - eliglustat	12/03/2020	n/a		PRAC Recommendation - maintenance
R/0022	Renewal of the marketing authorisation.	17/10/2019	16/12/2019	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Cerdelga in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.

II/0020	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/06/2019	n/a		
II/0021	Submission of the final report from study PKM14281 , A Randomized, Three-Period Crossover Study of Single and Repeated Doses for Three Different Strengths of Eliglustat in Healthy Adult, CYP2D6 Extensive and Poor Metabolizers, to characterize dose proportionality of 21, 42 and 84 mg eliglustat dosage strengths, in line with CHMP recommendation. Consequently section 5.2 of the Summary Product Characteristics (SmPC) was updated accordingly. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/04/2019	16/12/2019	SmPC and Annex II	Oral dosing of 84 mg eliglustat once daily was studied in CYP2D6 poor metabolisers (PMs). 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. 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.
PSUSA/10351 /201808	Periodic Safety Update EU Single assessment - eliglustat	14/03/2019	n/a		PRAC Recommendation - maintenance
IG/1003	A.1 - Administrative change - Change in the name and/or address of the MAH	20/12/2018	16/12/2019	SmPC, Labelling and PL	
IA/0017/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where	03/08/2018	n/a		

	batch control/testing takes place B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
II/0015/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/04/2018	07/06/2018	SmPC, Annex II, Labelling and PL	Results from Study POP13777 have been reflected in section 5.2 of the SmPC and allowed the following recommendations. In CYP2D6 extensive metabolisers with mild, moderate or severe renal impairment, no dosage adjustment is required and the recommended dose is 84 mg eliglustat twice daily. In CYP2D6 extensive metabolisers with end stage renal disease, Cerdelga is not recommended. In CYP2D6 intermediate metabolisers or poor metabolisers with mild, moderate or severe renal impairment or end stage renal disease, Cerdelga is not recommended. Results from Study POP13778 have been reflected in section 5.2 of the SmPC and allowed the following recommendations in section 4.2. In CYP2D6 extensive metabolisers with severe (Child-Pugh class C) hepatic impairment, Cerdelga is contraindicated. In CYP2D6 extensive metabolisers with moderate hepatic impairment (Child-Pugh class B), Cerdelga is not recommended. In CYP2D6 extensive metabolisers 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 with any degree of hepatic impairment, Cerdelga is not recommended and section 4.3. of the SmPC has been updated accordingly. In CYP2D6 extensive metabolisers with mild or moderate hepatic impairment taking a strong or moderate CYP2D6 inhibitor, Cerdelga is contraindicated. In CYP2D6 extensive metabolisers 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. Section 4.5 Interaction with other medicinal products and other forms of interaction has been updated concerning CYP2D6 inhibitors to include hepatic and renal impairment and refer to the updated sections 4.2, 4.3 and /or 4.4 as relevant. The key elements of prescriber's guide and patient alert card in the Annex II D have been updated to reflect the above recommendations in line with the SmPC revisions in section 4.2, 4.3 and 4.4.
PSUSA/10351 /201708	Periodic Safety Update EU Single assessment - eliglustat	08/03/2018	n/a		PRAC Recommendation - maintenance
PSUSA/10351 /201702	Periodic Safety Update EU Single assessment - eliglustat	28/09/2017	n/a		PRAC Recommendation - maintenance
II/0013	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/09/2017	26/01/2018	SmPC, Labelling and PL	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 majority of adverse reactions are mild and transient. The most frequently reported adverse reaction with Cerdelga is dyspepsia, in approximately 6% of the patients. About 2% of patients receiving Cerdelga in clinical trials permanently discontinued treatment due to any adverse reaction. The most frequently reported serious adverse reaction in clinical studies was syncope (0.8%). All events were associated with predisposing risk factors and appeared to be vasovagal in nature. None of these events led to discontinuation from the study.
II/0011	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	11/05/2017	26/01/2018	SmPC and PL	The applicant submitted the final study report for study GZGD00304 including efficacy and safety data up to 8 years. During the initial evaluation the data up to 4 years of treatment was assessed. This data showed that under continued eliglustat treatment patients showed improvement for haemoglobin, platelets, spleen volume, and liver volume. The 4 years data was already included in product information section 5.1. With this final study report the data showed that under continued eliglustat treatment patients remained stable or further improved up to month 96 for haemoglobin, platelets, spleen volume, and liver volume. The data beyond month 96 is too limited (as only 4

					patients had evaluable data) too draw firm conclusions. With respect to bone parameters, data up to month 96 shows that improved or stabilisation was observed for the dark marrow, femur T- and Z-scores, infarctions, lytic lesions. All patients at month 96 reported unrestricted mobility and no bone crisis. No new adverse drug reactions were identified in the report.
II/0010	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/03/2017	26/01/2018	SmPC and PL	Reports on the primary analysis period for the ENGAGE study and safety data from the EDGE study were submitted as part of the MAA and the results are reflected in the product information. This variation aimed at updating the product information with efficacy long-term data (up to 4.5 years) with Cerdelga from the final reports of the ENGAGE study. The EDGE study was designed to evaluate once (QD) versus twice daily (BID) dosing of eliglustat in patients with Gaucher disease type 1 (GD1). Results showed that a QD regimen does not favour over a BID regimen, and no dose recommendation should be included in the SmPC. No new safety issue were identified from both studies. Results from the ENGAGE study showed that 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 (1.1 g/dL [n=39], 1.4 g/dL [n=35] and 1.4 g/dL [n=12]), mean increase in platelet count (mm3; 58.5 % [n=39], 74.6% [n=35] and 86.8% [n=12]) , mean reduction in spleen

					volume (MN; 46.5% [n=38], 54.2% [n=32] and 65.6% [n=13]) and mean reduction in liver volume (MN; 13.7% [n=39], 18.5% [n=32] and 23.4% [n=13]). After 9 months of treatment, 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 randomised to placebo (p=0.0021). Five Cerdelga-treated patients (26%) achieved a reduction of at least 2 points in the BMB score after 9 months compared to none in the placebo treated patients. After 18 and 30 months of treatment, BMD 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.
PSUSA/10351 /201608	Periodic Safety Update EU Single assessment - eliglustat	09/03/2017	n/a		PRAC Recommendation - maintenance
II/0008	Update of section 5.1 of the SmPC to include 2, 3	23/02/2017	26/01/2018	SmPC	During the open-label long term treatment period

	and 4 years composite stability endpoint data based on the final results of the ENCORE study. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				(extension phase) of a study of Cerdelga in GD1 patients switching from ERT– Study 02607 (ENCORE), 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. For more information, including the 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, please refer to the Summary of Product Characteristics.
PSUSA/10351 /201601	Periodic Safety Update EU Single assessment - eliglustat	02/09/2016	n/a		PRAC Recommendation - maintenance
IB/0006/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	17/03/2016	n/a		

	authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
PSUSA/10351 /201507	Periodic Safety Update EU Single assessment - eliglustat	11/02/2016	n/a		PRAC Recommendation - maintenance
IA/0004	B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	23/09/2015	n/a		
IB/0003/G	This was an application for a group of variations. C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	04/09/2015	n/a		
IB/0002	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	20/08/2015	n/a		

IB/0001	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	11/03/2015	25/02/2016	SmPC, Labelling and PL	