Brineura

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
II/0039	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/11/2023	11/12/2023	SmPC, Annex II and PL	
IB/0044	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP -	30/11/2023	n/a		

[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).

	Replacement/addition of a site where batch control/testing takes place				
IA/0043/G	This was an application for a group of variations. B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	05/09/2023	n/a		
IB/0041	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	05/07/2023	n/a		
IA/0040/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-	18/04/2023	n/a		

	significant specification parameter (e.g. deletion of an obsolete parameter) B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits				
S/0038	Annual re-assessment.	23/02/2023	n/a		
IB/0037	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	06/04/2022	n/a		
R/0034	Renewal of the marketing authorisation.	27/01/2022	28/03/2022	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Brineura remains positive, but considers that an additional renewal is required for the following reasons: In the framework of the initial marketing authorisation under exceptional circumstances, a post-authorisation efficacy study (study 190-203) has been adopted as specific Obligation (SOP). An in-depth assessment of the totality of the data is needed at the time of submission of the final CSR, especially an in-depth assessment for efficacy and safety data for those patients <2 years of age. This will include the appropriateness of the current dosing recommendations with regard to efficacy and safety in younger children (below the age of 3 years), taking the available PK data into consideration. A second renewal of the marketing authorisation is required due to unfulfilled SOB, i.e. an uncompleted post-authorisation efficacy study, study 190-203

S/0035	4th annual re-assessment.	16/12/2021	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Brineura should be maintained.
PSUSA/10596 /202104	Periodic Safety Update EU Single assessment - cerliponase alfa	02/12/2021	n/a		PRAC Recommendation - maintenance
IB/0036	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	25/11/2021	n/a		
IA/0033/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	19/07/2021	n/a		
IB/0031	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	14/06/2021	n/a		
II/0029	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	29/04/2021	n/a		

IAIN/0030	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	06/04/2021	n/a		
II/0027	An update to the RMP, to change the final date for the completion of the Post-authorisation efficacy study 190-203 (final CSR), from 'July 2020' to "February 2023". C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/03/2021	12/05/2021	Annex II	The final date for the completion of the Post-authorisation efficacy study 190-203 (final CSR), from has been changed from 'July 2020' to "February 2023".
S/0028	3rd annual re-assessment	10/12/2020	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Brineura should be maintained.
PSUSA/10596 /202004	Periodic Safety Update EU Single assessment - cerliponase alfa	26/11/2020	n/a		PRAC Recommendation - maintenance
IB/0025	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	09/07/2020	n/a		
IB/0024	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/05/2020	12/05/2021	SmPC, Annex II and PL	
PSUSA/10596 /201910	Periodic Safety Update EU Single assessment - cerliponase alfa	14/05/2020	n/a		PRAC Recommendation - maintenance
IB/0023	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	06/04/2020	n/a		

	authorisation, including the RMP - Other variation				
II/0019	B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	02/04/2020	n/a		
PSUSA/10596 /201904	Periodic Safety Update EU Single assessment - cerliponase alfa	12/12/2019	13/02/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10596/201904.
IG/1141	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	12/12/2019	n/a		
S/0018	2nd annual re-assessment.	12/12/2019	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Brineura should be maintained.
IA/0016/G	This was an application for a group of variations. B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits	19/07/2019	n/a		

IAIN/0015	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	17/05/2019	n/a		
PSUSA/10596 /201810	Periodic Safety Update EU Single assessment - cerliponase alfa	16/05/2019	n/a		PRAC Recommendation - maintenance
IAIN/0014/G	This was an application for a group of variations. 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.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	21/03/2019	n/a		
IB/0012	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	18/12/2018	n/a		
II/0011	Please refer to the Recommendations section. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/12/2018	19/11/2019	SmPC and PL	The SmPC section 4.4 has been updated as follows: "Material degradation of the intracerebroventricular access device reservoir occurs after long periods of use according to preliminary results of benchtop testing and as observed in clinical trials with approximately 4 years of use. In two

					clinical cases, the ICV access devices did not show signs of failure at the time of infusion; however, after removal, material degradation of the devices were apparent and consistent with data from benchtop testing of ICV access devices. The access devices were replaced and patients resumed treatment with Brineura. Access device replacement should be considered prior to 4 years of regular administration of Brineura, however it must always be ensured, that the intracerebroventricular access device is used in accordance with the provisions of the respective medical device manufacturer." The PL has been updated accordingly.
II/0007	Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to update the safety information of Brineura in relation to device-related complications and meningitis, and to include meningitis as a possible adverse reaction, based on data collected from clinical trials and post-marketing experience. 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	06/12/2018	19/11/2019	SmPC and PL	Following a routine pharmacovigilance review, it has been observed intracerebroventricular access device-related infections, including sub-clinical infections and one case of meningitis, in patients treated with Brineura. As a result meningitis has been included in the SmPC as an adverse drug reaction with frequency "not known". Meningitis may present with the following symptoms: fever, headache, neck stiffness, light sensitivity, nausea, vomiting, and change in mental status. The signs and symptoms of device-related infections may not be apparent, therefore, cerebrospinal fluid samples should routinely be sent for testing to detect subclinical device infections.
PSUSA/10596 /201804	Periodic Safety Update EU Single assessment - cerliponase alfa	29/11/2018	n/a		PRAC Recommendation - maintenance
S/0009	1st annual re-assessment	15/11/2018	n/a		The CHMP, having reviewed the evidence of compliance

					with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Brineura should be maintained.
IB/0010	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	09/08/2018	n/a		
IA/0006/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	25/05/2018	n/a		
PSUSA/10596 /201710	Periodic Safety Update EU Single assessment - cerliponase alfa	17/05/2018	n/a		PRAC Recommendation - maintenance
IB/0005	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	17/04/2018	n/a		
IB/0004/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g.	13/04/2018	n/a		

	duplication of line)				
II/0001/G	This was an application for a group of variations. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product 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 batch control/testing takes place B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products	07/12/2017	20/11/2018	Annex II	
IB/0002/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of	06/12/2017	n/a		

	the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)				