Spravato

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/0026	Submission of the final study report for the non-interventional study PCSNSP002812 listed as a category 3 study in the RMP. This is a survey to assess the effectiveness of SPRAVATO educational materials in the European Union. The RMP version 8.1 was also submitted.	13/03/2025	n/a		Please refer to Scientific Discussion 'Spravato EMEA/H/C/004535/II/0026'

[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).

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
PSUSA/10825 /202403	Periodic Safety Update EU Single assessment - esketamine (for centrally authorised product only)	17/10/2024	12/12/2024	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10825/202403.
R/0023	Renewal of the marketing authorisation.	27/06/2024	22/08/2024	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Spravato in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0024	Update of section 4.8 of the SmPC in order to add 'hypotension' to the list of adverse drug reactions (ADRs) with frequency uncommon, based on a cumulative safety review. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/06/2024	22/08/2024	SmPC and PL	Update of section 4.8 to include "hypotension" as an uncommon adverse reaction with reported frequency based on clinical trials sources. The Package Leaflet (PL) is updated accordingly. In addition, section 4.2 is being amended to include administrative change as paediatric data are now available for esketamine. For more information, please refer to the Summary of Product Characteristics.
II/0020	Update of sections 4.4 and 4.8 of the SmPC in order to amend an existing warning on severe hepatic impairment and to include the long-term safety information based on final results from study 54135419TRD3008 (An Open-label Long-term Extension Safety Study of Esketamine Nasal Spray in Treatment-resistant Depression), listed as a category	11/04/2024	20/06/2024	SmPC	For more information, please refer to the Summary of Product Characteristics.

	3 study in the RMP. This was a multicenter, open-label, long-term extension safety study to evaluate safety, tolerability, and efficacy of esketamine in participants with TRD. The RMP version 5.1 has also been submitted. In addition, the MAH took the opportunity to introduce editorial changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0021	Update of the RMP to remove "use during pregnancy" as missing information from the list of safety concerns, with the consequential removal of the associated category 3 additional pharmacovigilance activity, the National Pregnancy Registry for Antidepressants. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	08/02/2024	n/a		Please refer to Scientific Discussion Spravato/H/C/004535/II/0021. For more information, please refer to the Summary of Product Characteristics.
II/0018	Update of section 5.1 of the SmPC in order to add efficacy and safety information based on the final results from study 54135419TRD3013 (ESCAPE). This is A Randomized, Open-label, Rater-Blinded, Active-Controlled, International, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Flexibly Dosed Esketamine Nasal Spray Compared	19/10/2023	20/06/2024	SmPC and PL	Update of section 5.1 of the SmPC in order to add efficacy and safety information based on the final results from a Randomized, Open-label, Rater-Blinded, Active-Controlled, International, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Flexibly Dosed Esketamine Nasal Spray Compared With Quetiapine Extended-Release in Adult and Elderly Participants With Treatment-Resistant

	With Quetiapine Extended-Release in Adult and Elderly Participants With Treatment-Resistant Major Depressive Disorder Who are Continuing a Selective Serotonin Reuptake Inhibitor/Serotonin-Norepinephrine Reuptake Inhibitor. In addition, the MAH took the opportunity to introduce minor editorial changes and to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Major Depressive Disorder Who are Continuing a Selective Serotonin Reuptake Inhibitor/Serotonin-Norepinephrine Reuptake Inhibitor. In addition, the MAH took the opportunity to introduce minor editorial changes and to update the list of local representatives in the Package Leaflet. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10825 /202303	Periodic Safety Update EU Single assessment - esketamine (for centrally authorised product only)	28/09/2023	n/a		PRAC Recommendation - maintenance
IB/0019/G	This was an application for a group of variations. B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	04/07/2023	20/06/2024	SmPC	
IB/0016/G	This was an application for a group of variations. B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	05/05/2023	n/a		

	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.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place				
PSUSA/10825 /202203	Periodic Safety Update EU Single assessment - esketamine (for centrally authorised product only)	13/10/2022	09/12/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10825/202203.
IAIN/0015	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	23/08/2022	09/12/2022	SmPC, Labelling and PL	
IB/0013	To extend the due date for a phase 3 study in the RMP. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/05/2022	n/a		To extend the due date for a phase 3 study in the RMP.
II/0012	Update to the SmPC Section 4.2, and Section 5.1, based on the findings in Chinese subjects from a recently completed efficacy Phase 3 Study in adult with treatment-resistant depression. C.I.4 - Change(s) in the SPC, Labelling or PL due to	12/05/2022	09/12/2022	SmPC	Update to the SmPC Section 4.2, and Section 5.1, based on the findings in Chinese subjects from a recently completed efficacy Phase 3 Study in adult with treatment-resistant depression. This update can be justified by the results of the completed Phase 3 study ESKETINTRD3006.

	new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10825 /202109	Periodic Safety Update EU Single assessment - esketamine (for centrally authorised product only)	07/04/2022	n/a		PRAC Recommendation - maintenance
PSUSA/10825 /202103	Periodic Safety Update EU Single assessment - esketamine (for centrally authorised product only)	30/09/2021	n/a		PRAC Recommendation - maintenance
IB/0008	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	21/06/2021	n/a		
IB/0009	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	04/05/2021	24/06/2022	SmPC, Annex II and PL	
PSUSA/10825 /202009	Periodic Safety Update EU Single assessment - esketamine (for centrally authorised product only)	09/04/2021	n/a		PRAC Recommendation - maintenance
II/0004	To update the Spravato Product Information at section 4.2 to replace the current dosing recommendation in patients with Japanese ancestry with a statement that efficacy of Spravato in Japanese patients has been studied but not established and to add information describing the study in section 5.1. The removal of the dosing recommendation for these patients is justified by the results of the completed Phase 2 study 54135419TRD2005. The MAH took also the opportunity to update the Product information according to latest QRD template (v. 10.1)	28/01/2021	26/02/2021	SmPC	Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-Var.No' SmPC new text Further to the results of the completed Phase 2 study 54135419TRD2005, the PI has been updated to remove the current dosing recommendation in patients with Japanese ancestry with a statement that efficacy of Spravato in Japanese patients has been studied but not established in section 4.2 and to add also information describing the study in section 5.1. For more information, please refer to the Summary of Product Characteristics.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0007	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	17/02/2021	n/a		
II/0001/G	This was an application for a group of variations. C.I.6(a): Extension of Indication to include a new indication for Spravato: Spravato, co-administered with oral antidepressant therapy, is indicated in adults with a moderate to severe episode of major depressive disorder, as acute short term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency (see section 5.1 for a description of the population studied). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.5 of the SmPC are updated. The RMP version 2.5 has also been agreed. B.II.e.5.a.2: Addition of a new pack size (multipack) of 24 nasal spray devices (multipack of 8 packs of 3 nasal spray devices) corresponding to 4 weeks of treatment in the new indication. The Package Leaflet and labelling are updated in accordance. In addition, the Marketing authorisation	10/12/2020	04/02/2021	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion 'Spravato-H-C-Product Number-II-Var.No' The group of variations requested amendments to the Summary of Product Characteristics, Annex II, Labelling, Package Leaflet and Annex IV and to the Risk Management Plan (RMP). Extension of Indication to include a new indication for Spravato as follows: "Spravato, co-administered with oral antidepressant therapy, is indicated in adults with a moderate to severe episode of major depressive disorder, as acute short term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency (see section 5.1 for a description of the population studied)" Addition of a new pack size (multipack) of 24 nasal spray devices (multipack of 8 packs of 3 nasal spray devices) corresponding to 4 weeks of treatment in the new indication. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.5 of the SmPC are updated. The RMP version 2.5 has also been agreed.

	holder (MAH) took the opportunity to clarify the wording in Annex II.D. 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 C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				The Package Leaflet and labelling are updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to clarify the wording in Annex II.D. Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed and accepted by the CHMP. In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Hungary.
PSUSA/10825 /202003	Periodic Safety Update EU Single assessment - esketamine (for centrally authorised product only)	01/10/2020	n/a		PRAC Recommendation - maintenance
IA/0005	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	24/09/2020	n/a		
IB/0003	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	21/07/2020	04/02/2021	SmPC	