Mysimba

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
PSUSA/10366 /202409	Periodic Safety Update EU Single assessment - naltrexone / bupropion	25/04/2025	17/07/2025	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10366/202409.
A20/0065		27/03/2025	22/05/2025	SmPC, Annex II and PL	

[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).

IAIN/0074	A.1 - Administrative change - Change in the name and/or address of the MAH	15/01/2025	22/05/2025	SmPC, Labelling and PL	
IB/0072/G	This was an application for a group of variations. B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF 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	13/01/2025	n/a		
II/0066	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	28/11/2024	n/a		
II/0063	To update sections 4.3, 4.4, 4.5 and 4.8 of the SmPC and related PIL sections following PRAC Assessment Report recommendations received during PSUSA/00010366/202209 procedure, on 21 April 2023: The MAH is requested to submit a Type II variation, within 30 days following the conclusion of the PSUSA, in order to enhance the existing risk	14/11/2024	22/05/2025	SmPC and PL	

	minimisation measures. This should include a comprehensive proposal to update and streamline the relevant wording on opioids in sections 4.3, 4.4, 4.5 and 4.8 of the SmPC (PL accordingly). In addition, the MAH should specify the opioid-free interval prior to starting NB treatment more precisely (e.g., whether for certain substances the period is longer than currently recommended). Furthermore, the MAH should clarify the current recommendation in the PL that a blood test (referring to opioids) may be carried out prior to starting NB and whether the SmPC should be updated accordingly. In the light of the above proposals to be made, the MAH should discuss possible further measures to address this risk. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH				
IA/0071	A.7 - Administrative change - Deletion of manufacturing sites	14/10/2024	n/a		
IB/0070/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change	26/06/2024	n/a		

	in the manufacturing process B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold 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 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				
PSUSA/10366 /202309	Periodic Safety Update EU Single assessment - naltrexone / bupropion	11/04/2024	n/a		PRAC Recommendation - maintenance
IAIN/0069/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	14/02/2024	n/a		
N/0068	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/01/2024	22/05/2025	PL	
IA/0064/G	This was an application for a group of variations. B.III.1.a.2 - Submission of a new/updated or	04/07/2023	n/a		

	deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer				
PSUSA/10366 /202209	Periodic Safety Update EU Single assessment - naltrexone / bupropion	26/04/2023	04/07/2023	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10366/202209.
IB/0062	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	27/02/2023	04/07/2023	SmPC and PL	
II/0054	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/02/2023	n/a		
IAIN/0059	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	15/12/2022	04/07/2023	Annex II and PL	
PSUSA/10366 /202109	Periodic Safety Update EU Single assessment - naltrexone / bupropion	22/04/2022	21/06/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10366/202109.
N/0057	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/05/2022	04/07/2023	PL	

II/0050	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	13/01/2022	n/a		
IA/0055/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 B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	21/12/2021	n/a		
IA/0052	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	10/12/2021	n/a		
N/0051	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/11/2021	21/06/2022	PL	
PSUSA/10366 /202009	Periodic Safety Update EU Single assessment - naltrexone / bupropion	22/04/2021	17/06/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10366/202009.
IA/0049/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 A.7 - Administrative change - Deletion of manufacturing sites	26/02/2021	n/a		

II/0042	B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a manufacturer of the AS supported by an ASMF	14/01/2021	n/a		
IAIN/0048/G	This was an application for a group of variations. 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.III.1.a.1 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from an already approved manufacturer	06/01/2021	n/a		
IA/0047/G	This was an application for a group of variations. B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	09/12/2020	n/a		
N/0045	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/11/2020	17/06/2021	PL	
II/0044/G	This was an application for a group of variations.	01/10/2020	17/06/2021	SmPC and PL	

	Update of product information resulting from PRAC Assessment Report request in PSUSA/00010366/201909: - Introduction of a warning concerning the interaction between Naltrexone/Bupropion and Digoxin in SmPC section 4.5 and related PL section. - Update of SmPC section 4.8 and related PL section on drug-induced lupus erythematosus with Naltrexone/Bupropion and its individual substance. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH				
N/0043	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/09/2020	17/06/2021	PL	
IB/0040/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting	13/08/2020	n/a		

	material/intermediate/reagent - Other variation				
PSUSA/10366 /201909	Periodic Safety Update EU Single assessment - naltrexone / bupropion	30/04/2020	03/07/2020		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10366/201909.
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)	19/06/2020	n/a		
N/0039	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/03/2020	03/07/2020	PL	
N/0037	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/03/2020	03/07/2020	PL	
IAIN/0038	B.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	17/01/2020	n/a		
R/0033	Renewal of the marketing authorisation.	14/11/2019	16/01/2020	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 Mysimba in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0029/G	This was an application for a group of variations. Group of variations consisting of: C.I.3.b: to update section 4.8 on the list of adverse drug reactions and their corresponding frequencies following the PRAC outcome on PSUR procedure	19/09/2019	24/10/2019	SmPC and PL	A single-dose pharmacokinetic study in patients with varying degrees of hepatic impairment showed that in patients with mild hepatic impairment, there was a modest increase in naltrexone concentrations. In patients with moderate and severe hepatic impairment, increases in the maximum concentration of naltrexone of ~6- and ~30-fold

	(PSUSA/10366/201709). C.I.4: to update sections 4.2, 4.4 and 5.2 of the SmPC to reflect the results from a phase I open label parallel study to evaluate the pharmacokinetics of a single oral dose of extended-release combination of naltrexone and bupropion in subjects with normal hepatic function or varying degrees of impaired hepatic function. Consequently, the recommendation to not use naltrexone/bupropion in patients with mild hepatic impairment has been replaced with dosing recommendations in these patients. Similar recommendations have also been included for patients with moderate and severe renal impairment. Section 4.4 has also been simplified by removing the warnings for contraindications as these are adequately reflected in section 4.3 of the SmPC. An updated RMP (version 12.4) was also submitted. In addition, the MAH took the opportunity to update the warning on lactose to be in accordance with EC guideline on Guideline on "Excipients in the labelling and package leaflet of medicinal products for human use". C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				were observed for the moderate and severe patients respectively. Naltrexone / bupropion is contraindicated in patients with severe hepatic impairment and is not recommended in patients with moderate hepatic impairment. In patients with mild hepatic impairment, the maximum recommended daily dose for naltrexone / bupropion should be reduced to two tablets (one tablet in the morning and one tablet in the evening). It is recommended that patients with mild hepatic impairment initiate treatment with one tablet in the morning for the first week of treatment, and escalate to one tablet in the morning and one tablet in the evening from Week 2 onwards.

IB/0034/G	This was an application for a group of variations. B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	19/10/2019	n/a		
N/0035	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/08/2019	24/10/2019	PL	
PSUSA/10366 /201809	Periodic Safety Update EU Single assessment - naltrexone / bupropion	26/04/2019	28/06/2019		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10366/201809.
IAIN/0032/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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 -	29/03/2019	28/06/2019	Annex II and PL	

	Not including batch control/testing				
IAIN/0030/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site 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	26/10/2018	n/a		
N/0028	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/07/2018	28/06/2019	PL	
PSUSA/10366 /201709	Periodic Safety Update EU Single assessment - naltrexone / bupropion	26/04/2018	02/07/2018	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10366/201709.
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/03/2018	02/07/2018	PL	
II/0023	Update of sections 4.2, 4.3, 4.4, 4.8 and 5.2 of the SmPC in order to update the dosage recommendation and safety information for patients with moderate renal impairment based on final results from study NaltrexBuprop-1006 - A Phase 1, Open-Label, Parallel Study to Evaluate the	14/12/2017	26/01/2018	SmPC and PL	The SmPC sections 4.2, 4.3, 4.4, 4.8 and 5.2 has been updated in order to update the dosage recommendation and safety information for patients with moderate renal impairment based on final results from study NaltrexBuprop-1006 - A Phase 1, Open-Label, Parallel Study to Evaluate the Pharmacokinetics of a Single Oral

	Pharmacokinetics of a Single Oral Dose of Extended-Release Combination of Naltrexone and Bupropion in Subjects With Normal Renal Function or Varying Degrees of Impaired Renal Function. 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				Dose of Extended-Release Combination of Naltrexone and Bupropion in Subjects With Normal Renal Function or Varying Degrees of Impaired Renal Function. The proposed update removes the contraindication for patients with severe renal impairment, provides new information on the posology and additional warning that the maximum recommended daily dose for naltrexone / bupropion should be reduced for this patient population. The PL have been updated accordingly.
PSUSA/10366 /201703	Periodic Safety Update EU Single assessment - naltrexone / bupropion	12/10/2017	08/12/2017	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10366/201703.
IB/0026	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)	05/12/2017	26/01/2018	SmPC	
IB/0024	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/11/2017	n/a		
IB/0022/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	11/10/2017	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IB/0021	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	21/09/2017	08/12/2017	SmPC, Labelling and PL	
II/0017	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/09/2017	n/a		
N/0020	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/09/2017	08/12/2017	PL	
IB/0018/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 batch control/testing takes place B.I.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation 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 B.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the	04/07/2017	n/a		

	relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)				
PSUSA/10366 /201609	Periodic Safety Update EU Single assessment - naltrexone / bupropion	21/04/2017	23/06/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10366/201609.
II/0015	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	22/06/2017	n/a		
II/0014	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	22/06/2017	n/a		
II/0010	Update of sections 4.4 and 4.8 of the SmPC to update existing warnings on seizures and blood pressure increase and to include abdominal discomfort, anxiety, dyspepsia, fatigue, hallucination, headache, hypertension, insomnia, irritability, and rash as adverse drug reactions for the Naltrexone/ Bupropion combination with a frequency unknown based on the results of study NB-CVOT (a Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Occurrence of Major Adverse Cardiovascular Events (MACE) in Overweight and Obese Subjects with Cardiovascular Risk Factors Receiving Naltrexone SR/Bupropion SR). In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.13 - Other variations not specifically covered	22/06/2017	08/12/2017	SmPC and PL	In a cardiovascular outcomes trial (CVOT) of patients at increased risk of a cardiovascular event, mean increases from baseline in systolic and diastolic blood pressure of approximately 1 mmHg compared to placebo were observed. This incidence of seizure, along with incidence of seizure in subjects who received naltrexone / bupropion at the time of interim analysis in a large, ongoing cardiovascular outcomes trial (CVOT), was no higher than the seizure rate with bupropion as a single agent at approved doses.

	elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0013/G	This was an application for a group of variations. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes 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 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.4.d - Change in the batch size (including batch size ranges) of the finished product - The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	01/06/2017	n/a		
N/0016	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/03/2017	23/06/2017	PL	

II/0011	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/02/2017	n/a		
IAIN/0008/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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 B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	09/11/2016	12/12/2016	SmPC	
PSUSA/10366 /201603	Periodic Safety Update EU Single assessment - naltrexone / bupropion	27/10/2016	n/a		PRAC Recommendation - maintenance
II/0005/G	This was an application for a group of variations. 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 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	15/09/2016	n/a		

	by new additional data to be submitted by the MAH where significant assessment is required				
N/0007	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/08/2016	12/12/2016	PL	
II/0003/G	This was an application for a group of variations. B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	26/05/2016	n/a		
N/0004	Inclusion of the list of local representatives at the end of the package leaflet. In addition, the MAH took the opportunity to make linguistic amendments in the Bulgarian, Croatian, Czech, Hungarian, Lithuanian, Polish, Romanian, and Slovenian labelling and package leaflets. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/05/2016	12/12/2016	PL	
PSUSA/10366 /201509	Periodic Safety Update EU Single assessment - naltrexone / bupropion	14/04/2016	n/a		PRAC Recommendation - maintenance

IAIN/0001	A.1 - Administrative change - Change in the name and/or address of the MAH	03/12/2015	12/12/2016	SmPC, Labelling and PL	