Brintellix

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
IB/0040	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/01/2024		SmPC	
II/0038	Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to include clinically relevant information on the efficacy, safety, tolerability, and	14/09/2023	18/10/2023	SmPC and PL	Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC to include clinically relevant information on the efficacy, safety, tolerability, and PK of vortioxetine in the paediatric

[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).

	PK of vortioxetine in the paediatric population based on final results from studies 12709A, 12712A and 12712B. Study 12709A is an interventional, randomized, double-blind, placebo-controlled, active-reference (fluoxetine), fixed-dose study of vortioxetine in paediatric patients aged 7 to 11 years, with Major Depressive Disorder (MDD) to evaluate efficacy and safety. Whereas studies 12712A and 12712B are 2 open-label, long-term safety and efficacy studies in children and adolescents: one 6-month extension study (Study 12712A) to Studies 12709A and 12710A, and one 18-month extension study (Study 12712B) to Study 12712A. In addition, updates are proposed in section 4.5 and package leaflet section 2 in relation to NSAIDs as well as updates to the Package leaflet section 4 to align SmPC wording on sexual dysfunction. 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				population based on final results from studies in children and adolescents. The Package Leaflet is updated accordingly. In addition, updates are proposed in the package leaflet in relation to NSAIDs as well as on sexual dysfunction to align SmPC wording. Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-Var.No' BRINTELLIX-/H/C/002717/II/0038 For more information, please refer to the Summary of Product Characteristics.
PSUSA/10052 /202209	Periodic Safety Update EU Single assessment - vortioxetine	25/05/2023	26/07/2023	SmPC, Labelling and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10052/202209.
II/0033	B.II.b.1.d - Replacement or addition of a manufacturing site for the FP - Site which requires an initial or product specific inspection	15/06/2023	n/a		

II/0037	Please refer to the Recommendations section 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		For more information, please refer to the Summary of Product Characteristics.
IB/0034	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	19/04/2022	n/a		
IA/0036	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	08/04/2022	n/a		
IA/0035/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.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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	08/04/2022	n/a		

IB/0031	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/09/2021	12/08/2022	SmPC and PL	
PSUSA/10052 /202009	Periodic Safety Update EU Single assessment - vortioxetine	20/05/2021	16/07/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10052/202009.
IAIN/0028	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/12/2020	16/07/2021	SmPC and PL	
II/0025	Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC to reflect the outcomes of the paediatric clinical study 12710A (a paediatric efficacy and safety study in adolescent MDD patients) and the study 12708A (paediatric pharmacokinetics and tolerability study in children and adolescent patients with DSM-IV diagnosis of depressive and anxiety disorder). In addition, the MAH took the opportunity to propose minor amendments to the labelling 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	17/09/2020	18/11/2020	SmPC, Labelling and PL	Please refer to Scientific Discussion 'Product Name-H-C-002717-II-Var.0025' SmPC new text Update of the Product Information to reflect the outcomes of the paediatric clinical study 12710A (a paediatric efficacy and safety study in adolescent MDD patients) and the study 12708A (paediatric pharmacokinetics and tolerability study in children and adolescent patients with DSM-IV diagnosis of depressive and anxiety disorder). For more information, please refer to the Summary of Product Characteristics.
PSUSA/10052 /201909	Periodic Safety Update EU Single assessment - vortioxetine	30/04/2020	03/07/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10052/201909.
IB/0027	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a	13/05/2020	n/a		

	re-test period/storage period supported by real time data				
IA/0026	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)	08/04/2020	n/a		
II/0022/G	This was an application for a group of variations. Update of section 5.1 of the SmPC to describe the effects of vortioxetine on treatment-emergent sexual dysfunction based on the outcome of the clinical studies 318 and 4001. Update of sections 4.4 and 5.2 to reflect the outcome of pharmacokinetic study 401 in subjects with severe hepatic impairment. Section 4.2 is also updated to add a cross reference to section 4.4 and 5.2 for hepatic impairment and section 4.4 wording for renal impairment is aligned to the one regarding hepatic impairment. 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	16/01/2020	03/07/2020	SmPC	In the iMAA of Brintellix (vortioxetine), to ensure a systematic evaluation of sexual dysfunction besides the spontaneous collection of adverse events (AEs), the Arizona Sexual Experiences Scale (ASEX) was used in a number of studies. In addition to the spontaneously reported AEs, the proportion of subjects who shifted from normal to abnormal according to the ASEX is described in the SmPC. These data indicate that the risk of developing Treatment-Emergent Sexual Dysfunction (TESD) with vortioxetine is low. In order to further investigate the risk of developing Treatment-Emergent Sexual Dysfunction (TESD) with vortioxetine, two active-comparator clinical studies 318 and 4001 were performed. The CHMP agrees to reflect the outcome of these studies in section 5.1 of the SmPC. Study 401 investigated the pharmacokinetics of vortioxetine and its metabolites in subjects with severe hepatic impairment. The CHMP agrees to reflect the outcome of the study in section 5.2 of the SmPC and update section 4.4 regarding the limited data available and caution to be exercised when treating patients with hepatic impairment.

IAIN/0023/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	20/09/2019	n/a		
PSUSA/10052 /201809	Periodic Safety Update EU Single assessment - vortioxetine	26/04/2019	28/06/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10052/201809.
R/0019	Renewal of the marketing authorisation.	20/09/2018	20/11/2018	SmPC, Labelling and PL	
IB/0020	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/07/2018	20/11/2018	SmPC and PL	
PSUSA/10052 /201709	Periodic Safety Update EU Single assessment - vortioxetine	12/04/2018	n/a		PRAC Recommendation - maintenance
IB/0017	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	06/12/2017	20/11/2018	SmPC, Labelling and PL	
IB/0014	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	18/05/2017	n/a		
PSUSA/10052 /201609	Periodic Safety Update EU Single assessment - vortioxetine	05/05/2017	n/a		PRAC Recommendation - maintenance

IA/0016/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) 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	03/05/2017	n/a		
IB/0015	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	27/04/2017	n/a		
PSUSA/10052 /201603	Periodic Safety Update EU Single assessment - vortioxetine	10/11/2016	11/01/2017	PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10052/201603.
IB/0011	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)	24/05/2016	11/01/2017	SmPC, Labelling and PL	
PSUSA/10052 /201509	Periodic Safety Update EU Single assessment - vortioxetine	14/04/2016	n/a		PRAC Recommendation - maintenance
PSUSA/10052 /201503	Periodic Safety Update EU Single assessment - vortioxetine	08/10/2015	n/a		PRAC Recommendation - maintenance

IB/0008	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	17/06/2015	24/02/2016	SmPC and PL	
IB/0007	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)	06/05/2015	24/02/2016	SmPC	
PSUSA/10052 /201409	Periodic Safety Update EU Single assessment - vortioxetine	10/04/2015	n/a		PRAC Recommendation - maintenance
II/0004	Update of section 5.1 of the SmPC with information on the effect of vortioxetine on certain aspects of cognitive function in Major Depressive Disorder. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/02/2015	24/02/2016	SmPC	Effect of vortioxetine on certain aspects of cognitive function in Major Depressive Disorder have been included in the SmPC further to data analysis, including results obtained with vortioxetine in Major Depressive Disorder (MDD) patients presenting with cognitive dysfunction.
IB/0005	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/12/2014	n/a		
PSUV/0003	Periodic Safety Update	23/10/2014	16/12/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0003.
IAIN/0002/G	This was an application for a group of variations. 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	07/03/2014	16/12/2014	SmPC, Labelling and PL	

	the range of the currently approved pack sizes 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 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				
IAIN/0001	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	07/03/2014	16/12/2014	SmPC, Labelling and PL	