a

Xeplion

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
WS/2405	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	25/05/2023		SmPC, Labelling 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).

	data				
IB/0056	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	13/03/2023	n/a		
IG/1499	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	21/03/2022	n/a		
IB/0053	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	11/03/2022	n/a		
PSUSA/2266/ 202106	Periodic Safety Update EU Single assessment - paliperidone	10/02/2022	n/a		PRAC Recommendation - maintenance
WS/1877	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/04/2021	07/06/2022	SmPC and PL	
IG/1257	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	21/07/2020	n/a		

WS/1833/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.z - Change in control of the 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	25/06/2020	n/a		
IG/1206	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	31/01/2020	n/a		
IA/0047	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	20/12/2019	n/a		
IA/0046	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	23/08/2019	n/a		
WS/1638	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.c.z - Container closure system of the AS - Other	11/07/2019	n/a		

	variation				
IA/0045	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	26/06/2019	n/a		
IG/1075/G	This was an application for a group of variations. B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	28/02/2019	n/a		
PSUSA/2266/ 201806	Periodic Safety Update EU Single assessment - paliperidone	14/02/2019	n/a		PRAC Recommendation - maintenance
WS/1417/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.5 of the SmPC in order to add information regarding concomitant use of paliperidone and risperidone with psychostimulants	13/09/2018	16/05/2019	SmPC, Labelling and PL	Caution is warranted in patients receiving both, psychostimulants (e.g., methylphenidate) and paliperidone concomitantly, as extrapyramidal symptoms could emerge when adjusting one or both medications. Gradual withdrawal of stimulant treatment is recommended. Catatonia has been introduced in the list of adverse drug reaction with a rare frequency.

	(in line with the CMDh recommendations for risperidone) and of section 4.8 of the SmPC to add catatonia as a new side-effect categorised as 'Rare'. The Package Leaflet is updated accordingly. The MAH took also the occasion to include editorial changes in the PI and to update the local representative for Ireland in the Package leaflet for Trevicta, Invega and Xeplion and Bulgaria for Risperidal Consta. The MAH also implemented the weekdays in section 5 of the annex IIIA for invega OPA blister according to the QRD guidance. 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				
WS/1359	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC in order to include somnambulism and sleep-related eating disorder under a rare and not known frequency, respectively, after post marketing reports analysis. The Package Leaflet is updated accordingly. In addition, for INVEGA/XEPLION/TREVICTA minor editorial changes have been introduced and the details of the local representatives in Portugal, Belgium Iceland,	31/05/2018	16/05/2019	SmPC and PL	

	Slovenia, Netherlands and Luxembourg are updated in the Package Leaflet. An update is also proposed to the INVEGA Package Leaflet in section 2 to add a standard statement concerning sodium content according to the Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. Updated wording to align to the Excipients Guideline is also proposed for Risperdal Oral, together with removing the brand name (West Medimop) for the vial adaptors for Risperdal Consta. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0035	Update of section 4.2 of the SmPC in order to add a dosage conversion table to provide guidance for healthcare professionals when switching patients from paliperidone ER tablets to paliperidone palmitate long acting injection (PP1M). An editorial update to clarify the contents of the treatment initiation pack has also been introduced in the Information for Users in the package leaflet to improve readability. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/01/2018	01/03/2018	SmPC and PL	During monthly maintenance treatment with Xeplion, patients previously stabilized on different doses of paliperidone prolonged-release tablets can attain similar paliperidone steady state exposure by injection. Please refer to the Summary of Product Characteristics for more information on specific doses of injected paliperidone depending on prior oral maintenance dose. Previous oral paliperidone or risperidone can be discontinued at the time of initiation of treatment with Xeplion injection. However, patients on higher doses (e.g. 9-12 mg daily) may benefit from gradual withdrawal due to a potentially lower exposure with Xeplion, and risk for relapse, during the first 6 months after the switch, especially after gluteal injection. Therefore, alternatively, it could be considered to give deltoid injections for the first 6

					months.
IA/0037/G	This was an application for a group of variations. 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.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	19/10/2017	n/a		
II/0031	Submission of the final study report of the "Post-Authorization Safety Study Using European Union Databases to Assess the Risk of Cardiovascular and Cerebrovascular Adverse Events in Elderly Patients Treated with Paliperidone Palmitate, Paliperidone Prolonged-Release, and Other Antipsychotics". 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		
IA/0036/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 A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder	10/08/2017	n/a		

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IB/0033/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	28/04/2017	n/a		
IA/0032	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)	28/02/2017	n/a		
II/0030	Update of section 4.8 of the Xeplion SmPC in order to reflect safety information after assessment of study R092670-SCA-3004 and the PP3M (TREVICTA, once 3-monthly paliperidone palmitate injection) studies R092670-PSY1005, R092670-PSY-3011 and R092670-PSY-3012; the Package Leaflet has been updated accordingly. Additional changes are proposed in order to align the Xeplion Product information with the TREVICTA Product Information (for which XEPLION is the reference medicinal product) following the assessment of the PP3M studies (ref. to TREVICTA procedure EMEA/H/C/004066/X/0007/G).	10/11/2016	28/04/2017	SmPC and PL	There were no new adverse drug reactions following the assessment of study R092670-SCA-3004 and the PP3M (once 3-monthly paliperidone palmitate injection) studies R092670-PSY1005, R092670-PSY-3011 and R092670-PSY-3012; only changes to frequencies of existing ADRs have been identified. 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/0027/G	This was an application for a group of variations. B.I.z - Quality change - Active substance - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	14/07/2016	n/a		
IG/0702	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	08/07/2016	n/a		
IA/0028	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	01/07/2016	n/a		
IB/0026	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/05/2016	28/04/2017	SmPC, Labelling and PL	
PSUSA/2266/201506	Periodic Safety Update EU Single assessment - paliperidone	14/01/2016	n/a		PRAC Recommendation - maintenance
R/0023	Renewal of the marketing authorisation.	22/10/2015	16/12/2015	SmPC, Annex II, Labelling	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and

				and PL	sufficiently demonstrated and therefore considers that the benefit/risk profile of Xeplion continues to be favourable. The CHMP is of the opinion that the renewal can be granted with unlimited validity.
WS/0760	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.8 of the SmPC in order to add a warning and update the safety information based on post-marketing experience on occurrence of hypersensitivity reactions in patients who have previously tolerated oral risperidone or paliperidone. The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to introduce minor editorial changes and to update the list of local representatives for Belgium and Luxemburg in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/07/2015	16/12/2015	SmPC and PL	Anaphylactic reactions in patients who have previously tolerated oral risperidone or oral paliperidone have been rarely reported during post marketing experience. If hypersensitivity reactions occur, discontinue use of paliperidone; initiate general supportive measures as clinically appropriate and monitor the patient until signs and symptoms resolve.
IG/0582/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.a - Introduction of, or change(s) to, the obligations and conditions of a marketing	01/07/2015	n/a		

	authorisation, including the RMP - Implementation of wording agreed by the competent authority				
WS/0700	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/06/2015	16/12/2015	SmPC and PL	
II/0019/G	This was an application for a group of variations. B.II.b.5.e - Change to in-process tests or limits applied during the manufacture of the finished product - Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product 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 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.z - Change in the manufacturing process of	26/03/2015	n/a		

	the finished or intermediate product - Other variation				
PSUV/0016	Periodic Safety Update	22/01/2015	23/03/2015	SmPC	Please refer to Xeplion/EMEA/H/C/2105/PSUV/16 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
IG/0531	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	05/03/2015	n/a		
II/0017	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	22/01/2015	n/a		
IAIN/0018	B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information	21/10/2014	23/03/2015	SmPC and PL	
IA/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	12/09/2014	n/a		
IAIN/0014	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	08/08/2014	n/a		
IA/0013/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	29/07/2014	n/a		

	changes to an approved test procedure 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				
IB/0012	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	01/07/2014	n/a		
PSUV/0011	Periodic Safety Update	09/01/2014	n/a		PRAC Recommendation - maintenance
II/0009	Update of section 4.2 of the Summary of Product Characteristics (SmPC) to support a change to the second initiation dose window from ± 2 days to ± 4 days. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/10/2013	03/12/2013	SmPC	Based on pharmacokinetic and safety reviews performed by the company, the CHMP accepted the modification of the second initiation dose window from ± 2 days to ± 4 days. Section 4.2 was updated as follows: - It is recommended that the second initiation dose of XEPLION be given one week after the first dose. To avoid a missed dose, patients may be given the second dose 4 days before or after the one-week (day 8) time point. Similarly, the third and subsequent injections after the initiation regimen are recommended to be given monthly. To avoid a missed monthly dose, patients may be given the injection up to 7 days before or after the monthly time point. If the target date for the second XEPLION injection (day 8 ± 4 days) is missed, the recommended reinitiation depends on the length of time which has elapsed since the patient's first injection.
WS/0403	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	25/07/2013	03/09/2013	SmPC and PL	The review of available post-authorisation safety data including the scientific literature revealed six case reports, including two with a timely relationship, of IFIS, a syndrome of eye problems during cataract surgery, in

	Update of sections 4.4 and 4.8 of the SmPC to add a new post-marketing adverse drug reaction of 'intraoperative floppy iris syndrome' (IFIS) and a related warning for risperidone and paliperidone containing medicinal products. Sections 2 and 4 of the package leaflet were amended accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				patients taking risperidone. While no reports were received for paliperidone, there is a biological plausibility that IFIS can occur also in paliperidone treated patients, as paliperidone is a derivative of risperidone and since both agents bind and block α1 adrenergic receptors, a known mechanism for this adverse drug reaction. Therefore, the CHMP agreed to add IFIS as an adverse drug reaction and to include a related warning in the product information of both risperidone and paliperidone containing medicinal products. The CHMP furthermore agreed to the distribution of a communication to ophthalmologists to alert them of this new risk.
IG/0341	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/07/2013	n/a		
II/0008	Update of section 4.8 of the Summary of Product Characteristics (SmPC) to add a new postmarketing adverse drug reaction (ADR) 'ileus' and a statement concerning 'anaphylactic reaction'. Section 4 of the Package Leaflet (PL) has been amended accordingly. In addition, the details of the local representatives are updated in the PL. The Product Information has also been updated in accordance with the latest QRD templates and editorial corrections were also made. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/07/2013	03/09/2013	SmPC, Annex II, Labelling and PL	Based on safety reviews performed by the MAH regarding ileus (lack of bowel muscle movement that causes blockage) and anaphylactic reaction, the CHMP accepted the inclusion of ileus as a rare adverse reaction in section 4.8 of the SmPC, given a case with positive dechallenge was reported suggesting a possible causal relationship between paliperidone and this event. The CHMP also agreed to include information on post-marketing cases of anaphylactic reactions with Xeplion, in patients who have previously tolerated oral risperidone or oral paliperidone.
II/0006/G	This was an application for a group of variations.	27/06/2013	n/a		

	To change the manufacturing process of the active substance and the heat sealing process of the container closure system for the active substance. To introduce an alternative quality control site for the active substance and to tighten bacterial endotoxin specification limits for the raw material, the intermediates and for the final active substance. B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product 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.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
IG/0213	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/08/2012	n/a		
II/0003	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) to harmonise the safety information regarding paliperidone, paliperidone palmitate and risperidone. Sections 2	24/05/2012	27/06/2012	SmPC, Annex II and PL	Considering the similar safety profile of paliperidone and risperidone containing medicinal products, the MAH proposed to harmonise the safety information of these products. As a result, alignment of existing warnings (on

	and 4 of the Package Leaflet (PL) have been amended accordingly. In addition, the details of the local representatives in Greece, Slovakia, Latvia, Cyprus and Luxembourg and information related to the administration of the product are updated in the PL. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				hyperglycaemia/diabetes mellitus, weight gain, hyperprolactinaemia), grouping of a number of adverse drug reactions (ADRs) terms , addition of new ADRs, updates of ADR frequencies were made for Xeplion. A new warning related to a risk of clinically significant low white blood cell count was added recommending monitoring or discontinuation of treatment in certain situations (e.g in case of severe neutropenia).
IB/0004/G	This was an application for a group of variations. 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.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size 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)	10/05/2012	n/a		
II/0001	Update of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) regarding the use of antipsychotics during the third trimester of pregnancy and risk of abnormal muscle movements and/or withdrawal symptoms in newborns in accordance with the PhVWP/CHMP class labelling	22/09/2011	12/10/2011	SmPC, Labelling and PL	There is evidence to suggest that the newborn babies of mothers treated with antipsychotics during the third trimester of pregnancy may suffer adverse effects (primarily extrapyramidal side effects and/or withdrawal effects). Whilst there is limited data available for some antipsychotics, this is likely to be a class effect. In addition

	recommended wording. Section 4 of the Labelling has been corrected regarding the treatment initiation pack. Details of the local representatives were also updated for Belgium, Bulgaria, Estonia, Italy, Latvia, Lithuania Luxembourg, Hungary, Austria, Portugal, Romania and Slovakia. Section 6 of the PL has also been updated to include the details of the manufacturer. Insertion of the marketing authorisation numbers were also made in the relevant sections of the Product Information. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				to the inclusion of neonatal drug withdrawal syndrome as listed adverse reaction, section 4.6 of the SmPC and section 2 of the PL were updated in accordance with the PhVWP/CHMP class labelling recommended wording, as follows: SmpC: Neonates exposed to antipsychotics (including paliperidone) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. PL: The following symptoms may occur in newborn babies, of mothers that have used paliperidone in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.
IG/0090/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	08/07/2011	n/a		