Invega

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
IA/0073	B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	09/07/2024		SmPC, Labelling and PL	
IA/0071	A.7 - Administrative change - Deletion of manufacturing sites	28/06/2022	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).

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		
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	05/05/2022	SmPC and PL	
IB/0067	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	19/10/2020	n/a		
IA/0066	B.I.c.z - Container closure system of the AS - Other variation	07/08/2020	n/a		
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		
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		

PSUSA/2266/201806	Periodic Safety Update EU Single assessment - paliperidone	14/02/2019	n/a		PRAC Recommendation - maintenance
IB/0062/G	This was an application for a group of variations. 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.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	03/10/2018	n/a		
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 (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	13/09/2018	06/06/2019	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.

	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				
IA/0061	B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	15/08/2018	06/06/2019	SmPC	
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, 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	31/05/2018	06/06/2019	SmPC and PL	

	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				
IB/0058	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	13/11/2017	n/a		
II/0056/G	This was an application for a group of variations. Update of section 4.2 and 4.9 of the SmPC in order to add 3 mg every other day dosing for patients with moderate and severe renal impairment and to delete the recommendation for gastric lavage in accordance with current best practices for management of overdose, respectively. Furthermore, the MAH is proposing the deletion of the Invega1.5 mg strength (all presentations) which has never been marketed in the EU. In addition, the details of the local representatives for Latvia, the Netherlands, Estonia and Lithuania are updated in the PL. The Company also proposes to combine the SmPCs for the different Invega strengths (3mg, 6mg, 9mg, 12mg) and to align the package leaflet to the latest QRD template (version 10.0).	20/07/2017	24/08/2017	SmPC, Annex II, Labelling and PL	For patients with moderate to severe renal impairment (creatinine clearance ☐ 10 to < 50 ml/min), the recommended initial dose of INVEGA is 3 mg every other day, which may be increased to 3 mg once daily after clinical reassessment.

	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 C.I.7.b - Deletion of - a strength				
IA/0057/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 or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient 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) 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)	10/08/2017	n/a		
IB/0054/G	This was an application for a group of variations.	19/04/2017	n/a		

	B.I.b.1.i - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Where there is no monograph in the European/National Ph. for the AS, a change in specification from in-house to a non-official/third country Ph. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
IB/0053	B.II.a.1.z - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Other variation	06/02/2017	n/a		
IA/0051	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	15/08/2016	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/0049	B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material	18/03/2016	n/a		
PSUSA/2266/201506	Periodic Safety Update EU Single assessment - paliperidone	14/01/2016	n/a		PRAC Recommendation - maintenance

IA/0048	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	12/11/2015	n/a		
II/0043	Extension of indication for Invega to include depressive symptom domain of schizoaffective disorder. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC have been updated. Minor editorial changes have been also introduced throughout the PI. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	23/04/2015	28/05/2015	SmPC, Labelling and PL	This variation extended the indication for Invega to include depressive symptom domain of schizoaffective disorder based on clinical data showing maintenance of symptom control and delay in relapse of psychotic, manic and depressive symptoms for the long acting injectable formulation of paliperidone. Please refer to Scientific Discussion Invega-H-C-746-II-43
IG/0549	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	29/04/2015	n/a		
IG/0526/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	04/03/2015	28/05/2015	Annex II and PL	

	site				
PSUV/0044	Periodic Safety Update	09/01/2015	n/a		PRAC Recommendation - maintenance
II/0037	Extension of indication to add the treatment of schizophrenia in adolescents 15 years and older. Consequential changes were made in sections 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 to include efficacy and safety information resulting from the submitted paediatric studies. The Package Leaflet has been amended accordingly. In addition, the list of local representatives in the Package Leaflet has been revised to amend contact details for the representatives of Luxembourg and Belgium. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	25/04/2014	23/05/2014	SmPC and PL	Please refer to the scientific discussion Invega H-000746-II-0037-AR.
PSUV/0041	Periodic Safety Update	09/01/2014	n/a		PRAC Recommendation - maintenance
IA/0042	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	07/10/2013	n/a		
WS/0403	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 to add a new post-marketing adverse drug reaction of	25/07/2013	26/08/2013	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 patients taking risperidone. While no reports were received for paliperidone, there is a biological plausibility that IFIS

	'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				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/0038	Update of section 4.8 of the Summary of Product Characteristics (SmPC) to add a new postmarketing adverse drug reaction (ADR) 'ileus'. 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 template. 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	26/08/2013	SmPC, Annex II and PL	Based on a safety review performed by the MAH regarding ileus (lack of bowel muscle movement that causes blockage), 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 relationship between paliperidone and this event.
IG/0213	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/08/2012	n/a		
II/0032	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) to harmonise the	24/05/2012	27/06/2012	SmPC and PL	Considering the similar safety profile of paliperidone and risperidone containing medicinal products, the MAH

	safety information regarding paliperidone, paliperidone palmitate and risperidone. A consequential change is made in section 4.2 of the SmPC. Sections 2 and 4 of the Package Leaflet (PL) have been amended accordingly. In addition, the details of the local representatives in Slovakia, Cyprus and Belgium are updated in the PL. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				proposed to harmonise the safety information of these products. As a result, alignment of existing warnings (on hyperglycaemia/diabetes mellitus, weight gain, hyperprolactinaemia), grouping of a number of adverse drug reactions (ADRs) terms , addition of new ADRs, updates of ADR frequencies and the paediatric safety information were made for Invega. 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/0035	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	12/06/2012	n/a		
R/0034	Renewal of the marketing authorisation.	15/03/2012	14/05/2012	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Invega continues to be favourable. The MAH will continue to submit annual PSURs, unless otherwise specified by the CHMP. The CHMP was also of the opinion that the renewal can be granted with unlimited validity.
IA/0033	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	16/12/2011	n/a		

II/0028	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 recommended wording. In addition, section 12 of the Labelling has been updated regarding the marketing authorisation numbers. Editorial changes were also made to Annex II and sections 3 and 6 of the Package Leaflet. Linguistic changes are also made in all language annexes. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	22/09/2011	12/10/2011	SmPC, Annex II, 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 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	08/07/2011	n/a		

	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				
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/04/2011	n/a	PL	
II/0023	Extension of indication to add: treatment of psychotic or manic symptoms of schizoaffective disorder. Effect on depressive symptoms has not been demonstrated. Extension of Indication	27/09/2010	08/04/2011	SmPC, Annex II and PL	Please refer to the scientific discussion Invega H-746-II-23-AR
II/0026/G	This was an application for a group of variations. to change the manufacturing process of the active substance, to change a test procedure and a specification limit for active substance and, to change the name of a manufacturer of the 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.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-	23/09/2010	28/09/2010		

	significant specification parameter (e.g. deletion of an obsolete parameter) 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 A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS				
IG/0023/G	This was an application for a group of variations. 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 C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD	21/09/2010	n/a	Annex II	
II/0025	Update of section 4.8 of the Summary of Product Characteristics (SPC) to add new adverse drug reactions (ADRs) based on 3 new clinical studies in patients with Bipolar I disorder and a post-marketing data review. Frequencies of some existing ADRs have also been updated. Section 4 of the Package Leaflet has been amended accordingly. In Section 4.5 of the	20/05/2010	01/07/2010	SmPC and PL	Based on additional safety data from clinical studies and post-marketing surveillance: - The following new ADRs were included in the SPC with corresponding frequencies: bundle branch block left (left heart block), vision blurred, constipation, dyspepsia (indigestion), nausea, stomach discomfort, flatulence,

	SPC, clozapine was added as other medicines known to lower the seizure threshold. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				oedema peripheral (increased fluid retention), urinary tract infection, pain in extremity, back pain, arthralgia (joint pain), muscle spasms, muscle twitching, muscle pains, trismus, torticollis, drooling, dysarthria (speech impediment), lethargy, cogwheel rigidity (stiff muscles like a cogwheel), parkinsonian gait (slow shuffling walk), transient ischaemic attack, breast tenderness, nasal congestion, pharyngolaryngeal pain (pain in the throat and upper part of the windpipe), pruritus, rash papular (rash with pimples on your skin), convulsion, pneumonia aspiration (pneumonia caused breathing stomach contents into lungs), urinary incontinence , urinary retention, angioedema (sudden swelling of lips and eyes along with difficulty breathing) and swollen tongue. - The frequencies of the following ADRs were updated: hyperprolactinaemia (high level of prolactin hormone in the blood), increased appetite, electrocardiogram QT prolonged (prolongation of QT interval from the heart), and retrograde ejaculation (ejaculation with semen flowing backwards into the bladder in males); anaphylactic reaction, hypersensitivity, parkinsonism, grand mal convulsion (convulsion with shaking movements and tense muscles),atrioventricular block first degree (block between 2 chambers of the heart), bradycardia (slow heart rate), ischaemia, salivary hypersecretion, gynaecomastia (abnormal breast enlargement in males), breast discharge, and irregular menstruation. In addition, clozapine was added as other medicines known to lower the seizure threshold.

IG/0007	C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	04/06/2010	n/a	Annex II	
II/0024	Update of the Detailed Description of the Pharmacovigilance System (DDPS). Update of DDPS (Pharmacovigilance)	18/02/2010	26/03/2010	Annex II	With this variation the MAH submitted a new version of the DDPS (version 005) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements.
II/0021	Update of sections 4.8 and 4.9 of the Summary of Product Characteristics (SPC) to reformat information related to the Adverse Drug Reactions (ADRs) in accordance with the SPC guideline and to add Torsade the Pointes and Ventricular Fibrillations as pharmacologically expected reactions of overdose, following CHMP conclusions on PSUR 3. Section 4 of the Package Leaflet (PL) was amended accordingly. Update of Summary of Product Characteristics and Package Leaflet	21/10/2009	23/11/2009	SmPC and PL	Further the assessment of the PSUR 3, the CHMP recommended that Torsade de Pointes should be mentioned in section 4.9 of the SPC in the list of pharmacologically expected reactions of overdose (following one reported case) and that the section 4.8 is reformatted according to the SPC guideline. In line with these recommendations, the MAH updated section 4.9 to include that torsades de pointes and ventricular fibrillation have been reported in association with overdose. Section 4.8 was reformatted to reflect the ADRs into one single table and a statement ("Paliperidone is the active metabolite of risperidone. The safety profile of risperidone may be pertinent") was added to highlight the link between paliperidone and risperidone.
II/0022	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SPC) in relation to a class-labelling on risk of venous thromboembolism (VTE) associated with antipsychotics at the CHMP request. Relevant sections of the Package Leaflet (PL) were amended accordingly. Update of Summary of Product Characteristics and	24/09/2009	05/11/2009	SmPC and PL	The Pharmacovigilance Working Party (PhVWP) considered a national review from a Member State on spontaneous reporting data and world-wide published literature on antipsychotics and the risk of venous thromboembolic events (VTE). Despite the limitations of both sources of information (data from literature is limited by the lack of randomised controlled trial data and the heterogeneity of completed published studies; post marketing data is limited

	Package Leaflet				by potential confounding factors such as sedation and weight gain which are commonly present in antipsychotic users), the PhVWP concluded that an association between VTE and antipsychotics cannot be excluded. The PhVWP concluded that it was not possible to distinguish risk between different drugs and therefore there was no justification for warnings for VTE just for a few drugs. Following the PhVWP conclusions, the CHMP recommended the inclusion of the proposed PhVWP class labelling into the Invega SPC/PL. The class effects section was updated to add venous thromboembolism including cases of pulmonary embolism and deep vein thrombosis (frequency unknown) and the following new warning was included in the SPC: - Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with INVEGA and preventive measures undertaken.
II/0020	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SPC) to include information on priapism based on postmarketing surveillance and the relationship with risperidone. Section 4 of the Package Leaflet (PL) has been amended accordingly. Annex II was also updated to reflect the new version number of the risk management plan. Update of Summary of Product Characteristics and Package Leaflet	29/05/2009	07/07/2009	SmPC, Annex II and PL	Antipsychotics drugs with ?-adrenergic blocking effects have been reported to induce priapism. No cases of priapism were reported in the clinical trials with paliperidone. However, cumulatively, 4 cases of priapism have been reported during postmarketing surveillance, including one case suggestive of a drug-event relationship in a patient who previously experienced priapism with risperidone. On this basis, the CHMP considered it acceptable to reflect the information on priapism into the SPC and PL of paliperidone including a warning that patients should be informed to seek urgent medical care in

					case that priapism has not been resolved within 3-4 hours.
X/0003	Annex I_2.(c) Change or addition of a new strength/potency	23/10/2008	12/01/2009	SmPC, Labelling and PL	
II/0018	Update of the section 4.2 of the Summary of Product Characteristics to update the dosing recommendations in patients with renal impairment and to include a new recommendation for dose titration. Also minor editorial changes were implemented in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	23/10/2008	12/01/2009	SmPC and PL	Section 4.2 of the SPC (Posology and Method of Administration) for the currently approved strengths of INVEGA (3, 6, 9 and 12 mg) was updated with information regarding the dosing recommendations in patients with renal impairment and a new recommendation for dose titration. The variation is in accordance with a line extension for INVEGA (EMEA/H/C/746/X/03) to include an additional dosage strength of 1.5 mg, in order to meet the needs for dose adjustment in patients with renal impairment. The amendments include an upper limit dose of 6 mg once daily for patients with mild renal impairment and an update to the dosage recommendation for patients with moderate to severe renal impairment (from a creatinine clearance of 10 ml/min) to 1.5 mg (new strength) every day instead of 3 mg every other day. The PL was updated accordingly. Furthermore, details of the local representatives in Malta and Estonia have also been updated in the PL.
IB/0017	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	14/05/2008	14/05/2008	SmPC, Labelling and PL	
IB/0016	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	14/05/2008	14/05/2008	SmPC, Labelling and PL	

IB/0015	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	14/05/2008	14/05/2008	SmPC, Labelling and PL	
IB/0014	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	14/05/2008	14/05/2008	SmPC, Labelling and PL	
IB/0013	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	14/05/2008	14/05/2008	SmPC, Labelling and PL	
IB/0012	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	14/05/2008	14/05/2008	SmPC, Labelling and PL	
IB/0011	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	14/05/2008	14/05/2008	SmPC, Labelling and PL	
IB/0010	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	14/05/2008	14/05/2008	SmPC, Labelling and PL	
IB/0009	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	14/05/2008	14/05/2008	SmPC, Labelling and PL	
IB/0008	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	14/05/2008	14/05/2008	SmPC, Labelling and PL	
IB/0007	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	14/05/2008	14/05/2008	SmPC, Labelling and PL	

IB/0006	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	14/05/2008	14/05/2008	SmPC, Labelling and PL	
IB/0004	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	24/04/2008	n/a		
II/0002	Update of section 4.5 of the Summary of Product Characteristics (SPC) to reflect the results of a drug interaction study (R076477-BIM-1001) between paliperidone and carbamazepine. Editorial changes were made in sections 4.3 and 5.2 of the SPC and in the labelling. The details for some of the local representatives were also updated in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	19/03/2008	22/04/2008	SmPC, Labelling and PL	Based on the review of the interaction study between paliperidone and carbamazepine, the SPC was amended to include the following: - Co-administration of INVEGA once daily with carbamazepine 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state Cmax and AUC of paliperidone; this decrease is caused, to a substantial degree, by a 35% increase in renal clearance of paliperidone likely as a result of induction of renal P-gp by carbamazepine. - A minor decrease in the amount of drug excreted unchanged in the urine suggested that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. - Larger decreases in plasma concentrations of paliperidone could occur with higher doses of carbamazepine. - On initiation of carbamazepine, the dose of INVEGA should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of INVEGA should be re-evaluated and decreased if necessary. - It takes 2-3 weeks for full induction to be achieved and upon discontinuation of the inducer the effect wears off over a similar time period.

					- Other medicinal products or herbals which are inducers, e.g. rifampicin and St John´s wort (Hypericum perforatum) may have similar effects on paliperidone.
IA/0001	IA_23_b_Change in source of excip./reagent to veg./synthetic material - other cases	13/11/2007	n/a		