Imnovid

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/0051	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	25/08/2023		Annex II	
II/0047	Update of section 4.4 of the SmPC, Annex IID and Article 127a and the tools/documents included in the	08/06/2023	11/08/2023	SmPC and	Not applicable

[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).

	Educational Healthcare Professional Kit, in order to harmonise the terminology utilised in the RMP and PI documents relating to the safety concern of teratogenicity and its risk minimisation measure of the Pregnancy Prevention Plan across the 3 IMiDs. These proposed changes will only have a limited impact on the National Competent Authority (NCA)-approved content/text of the educational materials, and the key messages to the HCP and patients. Furthermore, the regulatory obligations regarding the PPP will not be impacted. The updated RMP version 16.5 was provided. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data			Annex II	
II/0050	Update of sections 4.8 and 5.1 of the SmPC in order to update efficacy and safety information following the assessment of II/0031/G based on OS results from study CC-4047-MM-007 listed as PAES in the Annex II; this is to further investigate the efficacy of pomalidomide in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/07/2023		SmPC and Annex II	For more information, please refer to the Summary of Product Characteristics.

R/0049	Renewal of the marketing authorisation.	23/02/2023	24/04/2023	SmPC, Annex II and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Imnovid in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IA/0048	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	23/08/2022	n/a		
PSUSA/10127 /202102	Periodic Safety Update EU Single assessment - pomalidomide	14/10/2021	09/12/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10127/202102.
IAIN/0046/G	This was an application for a group of variations. 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 A.7 - Administrative change - Deletion of manufacturing sites	27/10/2021	14/10/2022	Annex II and PL	
IB/0045	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	06/10/2021	09/12/2021	Annex II	
N/0043	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/10/2021	09/12/2021	Labelling and PL	

IA/0044	B.II.a.4.a - Change in coating weight of oral dosage forms or change in weight of capsule shells - Solid oral pharmaceutical forms	13/08/2021	09/12/2021	SmPC and Labelling	
T/0041	Transfer of Marketing Authorisation	20/05/2021	24/06/2021	SmPC, Labelling and PL	
IAIN/0040	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/11/2020	24/06/2021	SmPC and PL	
II/0038	Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC with information from a paediatric study in patients aged 4 to 18 years with recurrent or progressive high-grade glioma, medulloblastoma, ependymoma or diffuse intrinsic pontine glioma (DIPG) with primary location in the CNS. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/11/2020	24/06/2021	SmPC	Please refer to Scientific Discussion EMEA/H/C/002682/II/0038.
IA/0039	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	28/07/2020	n/a		
II/0036/G	This was an application for a group of variations. Group of two type II variations to update sections 4.2, 4.4 and 4.8 of the SmPC and section 4 of the PL	30/04/2020	03/06/2020	SmPC, Annex II and PL	A Safety Topic Review was undertaken to evaluate reports of anaphylactic reactions in patients treated with pomalidomide, identified as a potential safety signal during routine signal detection activities. The SmPC has been

	with information on anaphylactic reactions with a not known frequency and section 4.8 of SmPC with hypothyroidism following a safety review. This group also includes a Type IB Variation to update section 6.6 of the SmPC in order to include recommendations to minimise the risk of unintended occupational exposures in healthcare professionals. The MAH has also proposed minor updates to section 4.4 of the SmPC and Annex IID regarding the educational materials, prescribing and dispensing restrictions in order to provide more clarity about the recommended maximum duration of treatment. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation 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				updated to include information on anaphylactic reactions in sections 4.2, 4.4 and 4.8 (with a not known frequency). Patients with a prior history of serious allergic reactions associated with thalidomide or lenalidomide, may be at higher risk of hypersensitivity and should not receive pomalidomide. Pomalidomide must be discontinued permanently for angioedema and anaphylactic reactions; widespread rash, high body temperature, enlarged lymph nodes and other body organs involvement (Drug Reaction with Eosinophilia and Systemic Symptoms which is also known as DRESS or drug hypersensitivity syndrome, Toxic Epidermal Necrolysis or Stevens-Johnson Syndrome). Patients should be advised of the signs and symptoms of these reactions by their prescribers and should be told to seek medical attention immediately if they develop these symptoms. Patients with a history of severe rash associated with thalidomide treatment should not receive pomalidomide. Cases of hypothyroidism which may cause symptoms such as tiredness, lethargy, muscle weakness, slow heart rate, weight gain have been reported (SmPC section 4.4) as an uncommon side-effect. Optimal control of co-morbid conditions influencing thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended. Section 6.6 of the SmPC is updated in order to include a recommendation to wear disposable gloves to minimise the risk of unintended occupational exposures in healthcare professionals and caregivers. Women who are pregnant or suspect they may be pregnant should not handle the blister or capsule. The MAH has also proposed minor updates to section 4.4 of

					the SmPC and Annex IID regarding the educational materials, prescribing and dispensing restrictions in order to provide more clarity about the recommended maximum duration of treatment and handling of the product. The SmPC sections 4.2, 4.4, 4.8 and 6.6 and Annex IID have been updated. The PL section 4 on allergic reaction and hypothroidism side effects has been updated accordingly. For more information, please refer to the Summary of Product Characteristics.
IA/0037	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	13/11/2019	n/a		
PSUSA/10127 /201902	Periodic Safety Update EU Single assessment - pomalidomide	05/09/2019	n/a		PRAC Recommendation - maintenance
IB/0034	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	18/06/2019	n/a		
II/0031/G	This was an application for a group of variations. Extension of indication for Imnovid to include a new indication: treatment in combination with bortezomib and dexamethasone of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Annex II is also updated to include a new post-authorisation	28/03/2019	13/05/2019	SmPC, Labelling and PL	Please refer to the published Assessment Report Imnovid-H-2682-II-31/G.

	efficacy study (PAES) as an obligation of the marketing authorisation. As a further consequence, new 14-capsule pack sizes for the 1 mg, 2 mg, 3 mg and 4 mg Imnovid strengths were included to support the new proposed posology and pomalidomide dose modification. The SmPC, Labelling and Package leaflet are updated in accordance. Finally, section 5.1 of the SmPC is updated in order to update the information on pomalidomide mechanism of action based on literature data. The RMP version 15.1 has also been updated. 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 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 B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				

IA/0033	A.7 - Administrative change - Deletion of manufacturing sites	28/03/2019	13/05/2019	Annex II and PL	
IAIN/0032/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	19/11/2018	13/05/2019	Annex II and PL	
T/0030	Transfer of Marketing Authorisation	13/07/2018	28/09/2018	SmPC, Labelling and PL	
PSUSA/10127 /201802	Periodic Safety Update EU Single assessment - pomalidomide	06/09/2018	n/a		PRAC Recommendation - maintenance
R/0028	Renewal of the marketing authorisation.	26/04/2018	11/07/2018	SmPC, Annex II, Labelling and PL	
II/0027	Update of sections 4.2, 4.4, and 4.8 of the SmPC in order to add new ADRs SJS, TEN and DRESS following a review of reports on severe skin reactions. The Package Leaflet is updated	08/03/2018	23/04/2018	SmPC and PL	Angioedema and severe dermatologic reactions including Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported with the

	accordingly. The RMP version 12.0 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				use of pomalidomide. Patients should be advised of the signs and symptoms of these reactions by their prescribers and should be told to seek medical attention immediately if they develop these symptoms. Pomalidomide must be discontinued for exfoliative or bullous rash, or if SJS, TEN or DRESS is suspected, and should not be resumed following discontinuation for these reactions. Patients with a history of severe rash associated with lenalidomide or thalidomide should not receive pomalidomide.
II/0025	Submission of a biomarker analysis report based on the clinical study CC-4047-MM-010 following a recommendation from the CHMP at the time of the initial authorisation. 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		
PSUSA/10127 /201702	Periodic Safety Update EU Single assessment - pomalidomide	01/09/2017	n/a		PRAC Recommendation - maintenance
IAIN/0026	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	18/08/2017	23/04/2018	Annex II	
PSUSA/10127 /201608	Periodic Safety Update EU Single assessment - pomalidomide	09/03/2017	n/a		PRAC Recommendation - maintenance
IB/0022	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	13/09/2016	24/05/2017	SmPC, Annex	

	authorisation, including the RMP - Other variation			II and PL	
PSUSA/10127 /201602	Periodic Safety Update EU Single assessment - pomalidomide	02/09/2016	n/a		PRAC Recommendation - maintenance
IA/0021/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 B.I.c.2.a - Change in the specification parameters and/or limits of the immediate packaging of the AS - Tightening of specification limits	24/08/2016	n/a		
II/0018	Update of sections 4.2, 4.9 and 5.2 of the SmPC in order to update the safety information based on meta-analysis of two renal impairment studies (CC-4047-MM-008 and CC-4047-MM-013) in fulfilment of the post-authorisation measure MEA 004.1. The Package Leaflet is updated accordingly. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/06/2016	29/07/2016	SmPC and PL	No dose adjustment of pomalidomide is required for patients with renal impairment. On haemodialysis days, patients should take their pomalidomide dose following haemodialysis. Pomalidomide doses as high as 50 mg as a single dose in healthy volunteers and 10 mg as once-daily multiple doses in multiple myeloma patients have been studied without reported serious adverse events related to overdose. Pomalidomide was removed by haemodialysis. Population pharmacokinetic analyses showed that the pomalidomide pharmacokinetic parameters were not remarkably affected in renally impaired patients (defined by creatinine clearance or estimated glomerular filtration rate [eGFR]) compared to patients with normal renal function (CrCl ≥60 mL/minute). Mean normalized AUC exposure to pomalidomide was 98.2% with a 90% confidence interval

					[77.4% to 120.6%] in moderate renal impairment patients (eGFR ≥30 to ≤45mL/minute/1.73 m2) compared to patients with normal renal function. Mean normalized AUC exposure to pomalidomide was 100.2% with a 90% confidence interval [79.7% to 127.0%] in severe renal impairment patients not requiring dialysis (CrCl <30 or eGFR <30 mL/minute/1.73 m2) compared to patients with normal renal function. Mean normalized AUC exposure to pomalidomide increased by 35.8% with a 90% CI [7.5% to 70.0%] in severe renal impairment patients requiring dialysis (CrCl <30mL/minute requiring dialysis) compared to patients with normal renal function. The mean changes in exposure to pomalidomide in each of these renal impairment groups are not of a magnitude that require dosage adjustments.
IB/0019	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)	06/07/2016	24/05/2017	SmPC	
II/0016/G	This was an application for a group of variations. This is a grouped application of 3 Type II variations based on three clinical pharmacology study reports as follows: • Update of sections 4.2 and 5.2 of the SmPC to reflect clinical data from a hepatic impairment study (CC-4047-CP-009) on pomalidomide exposure in subjects with hepatic impairment • Update of sections 5.2 of the SmPC to reflect data from study CC-4047-CP-011 on the effect of food, smoking and elderly age on pomalidomide exposure	26/05/2016	24/06/2016	SmPC and PL	As requested by CHMP at the time of the initial MA, the MAH carried out a study in non-malignant subjects to evaluate pomalidomide use in patients with hepatic impairment. The final results of this study were submitted with this variation. Sections 4.2 and 5.2 of the SmPC were updated to reflect the clinical finding that hepatic impairment has a modest effect on the pharmacokinetics of pomalidomide, thus no adjustment of the starting dose of pomalidomide is required for patients with hepatic impairment. In addition, the final study report of a study that evaluated

	• Update of sections 4.2, 4.5 and 5.2 of the SmPC (& PL) to reflect data from study CC-4047-CP-012 on co-administration of pomalidomide and CYP1A2 inhibitors The MAH is taking this opportunity to propose four other minor modifications to the SmPC text that do not require assessment: a. Addition of the SmPC of instructions on discontinuation of pomalidomide therapy in section 4.2 (text added for consistency with the same message already approved for the warnings section 4.4 for angioedema/rash in the context of procedure EMEA/H/C/PSUSA/00010127/201408) b. Correction of data in SmPC section 4.5 and 5.2 from the clinical pharmacology study CC-4047-CP-008 to reflect AUC0–∞ instead of the AUC0–t c. Minor editorial change to SmPC 4.2 statement "There is no relevant use of Imnovid in children aged 0-17 years for the indication of multiple myeloma." d. Replacing the term 'patients' with 'subjects', as per QRD template 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.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				the PK of pomalidomide administered with the CYP1A2 inhibitor fluvoxamine was submitted. Fluvoxamine co-administration resulted in an approximate doubling of exposure to pomalidomide. Sections 4.2, 4.5 and 5.2 of the SmPC were updated to instruct that if strong inhibitors of CYP1A2 (e.g. ciprofloxacin, enoxacin and fluvoxamine) are co-administered with pomalidomide, the dose of pomalidomide should be reduced by 50%. Finally, the MAH conducted a study to evaluate the effects on pomalidomide PK of food in elderly people. This study also evaluated CYP1A2 induction by comparing PK parameters in smokers and non-smokers. The SmPC section 5.2 information that pomalidomide can be taken without regard to food intake only underwent minor amendments, and its spirit remained unchanged. Wording informing that administration of pomalidomide in smokers had no clinically relevant effect on exposure to pomalidomide compared to that exposure to pomalidomide observed in non-smokers was also added to Section 5.2.

PSUSA/10127 /201508	Periodic Safety Update EU Single assessment - pomalidomide	01/04/2016	26/05/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10127/201508.
IB/0017	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	05/02/2016	n/a		
IA/0015	A.7 - Administrative change - Deletion of manufacturing sites	02/12/2015	n/a		
PSUSA/10127 /201502	Periodic Safety Update EU Single assessment - pomalidomide	24/09/2015	19/11/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10127/201502.
II/0012	Submission of the final study report of the companion study CC-4047-MM-003/C. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	06/08/2015	n/a		N/A
IG/0590	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	22/07/2015	n/a		
PSUSA/10127 /201408	Periodic Safety Update EU Single assessment - pomalidomide	26/03/2015	27/05/2015	SmPC, Annex II and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10127/201408.

II/0008	Submission of a thorough QT (TQT) study in healthy volunteers (CC-4047-CP-010) included in the RMP (MEA 003). No changes to the PI were proposed. This variation proposed amendments to the Risk Management Plan (RMP). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	18/12/2014	n/a		
IB/0010/G	This was an application for a group of variations. B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold 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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	17/12/2014	n/a		

II/0005	Update of Section 4.8 of the SmPC to include the ADRs 'pancytopenia' and 'tumour lysis syndrome'. The Package Leaflet is updated accordingly. In addition, editorial changes are included in Sections 4.2, 5.3, 6.1 of the SmPC and the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/11/2014	27/05/2015	SmPC and PL	Pancytopaenia and tumour lysis syndrome (TLS) have been seen in clinical trials and the post-marketing setting in association with pomalidomide use. A causal association between pomalidomide and these safety concerns seems likely. Although some cases of pancytopaenia were confounded in the setting of advanced multiple myeloma, supportive factors for pomalidomide causality include the temporal relationship, positive dechallenge followed by negative rechallenge with pomalidomide dose reduction and biological plausibility. With regards to TLS, there was a close relationship to the initiation of pomalidomide therapy and also biological plausibility. Only 1 report of TLS was confounded by concomitant carfilzomib therapy. Both reactions are listed for the related immunomodulatory compounds, lenalidomide and thalidomide. Pancytopaenia and tumour lysis syndrome were added to section 4.8 of the pomalidomide SmPC. This does not alter the benefit-risk balance of pomalidomide.
PSUV/0006	Periodic Safety Update	25/09/2014	19/11/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0006.
IB/0007/G	This was an application for a group of variations. 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) B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	28/07/2014	26/08/2014	SmPC, Labelling and PL	

II/0003	Update of section 5.2 of the SmPC following CHMP request, based on the results of population pharmacokinetics analysis to address a post authorisation measure included in the RMP. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	24/07/2014	26/08/2014	SmPC	Based on population PK analysis using a two-compartment model, healthy subjects and multiple myeloma patients had comparable apparent clearance (CL/F) and apparent central volume of distribution (V2/F). In peripheral tissues, pomalidomide was preferentially taken up by tumors with apparent peripheral distribution clearance (Q/F) and apparent peripheral volume of distribution (V3/F) 3.7-fold and 8-fold higher, respectively, than that of healthy subjects.
IA/0004	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	18/02/2014	n/a		
II/0002/G	This was an application for a group of variations. Submission of the results of: study CC-4047-DMPK-1586 on in vitro assessment of pomalidomide as an inhibitor of P glycoprotein using Caco-2 cells (MEA 006); Study CC-4047-DMPK-1653 on substrate potential in OATP1B1 and OATP1B3 expressing HEK293 cells (MEA 007); Study CC-4047-CP-008, a phase I open label study to evaluate the effect of CYP 450 and P-gp inhibition and induction on the pharmacokinetics of pomalidomide in healthy male subjects. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered	23/01/2014	n/a		Study CC-4047-DMPK-1586 was an in vitro assessment of pomalidomide as an inhibitor of P-glycoprotein using Caco-2 cells. This study confirmed that pomalidomide is not an inhibitor of Pgp and therefore interactions with drugs that are substrates for this transporter would not be expected. Study CC-4047-DMPK-1653 was conducted in HEK293 cells (expressing OATP1B1 and OATP1B3) and control cells to evaluate the substrate potential of pomalidomide. The cell uptake studies demonstrate that pomalidomide is not a substrate for the hepatic uptake transporters OATP1B1 and OATP1B3, therefore interactions with drugs that are substrates or inhibitors of this transporter would not be expected. The final results of Study CC-4047-CP-008, a phase 1 open-label study to evaluate the effect of CYP and Pgp inhibition and induction on the pharmacokinetics of pomalidomide in healthy male subjects, were also

	elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				submitted. The results confirm the preliminary data submitted at the time of the initial marketing authorisation. Co-administration of a strong CYP3A4/Pgp inhibitor (ketoconazole) or CYP3A4 inducer (carbamazepine) with pomalidomide had no clinically relevant effect on mean exposure to pomalidomide. Co-administration of a strong CYP1A2 inhibitor (fluvoxamine) with pomalidomide in the presence of a strong CYP3A4 inhibitor approximately doubled the mean exposure to pomalidomide. Pomalidomide was generally well tolerated by healthy subjects when administered as single 4-mg oral doses with multiple oral doses of ketoconazole, fluvoxamine, and/or carbamazepine. The current wording that 'If strong inhibitors of CYP1A2 are co-administered with pomalidomide, patients should be closely monitored for the occurrence of side-effects' is therefore judged to be sufficient and no changes are required to the product information.
IAIN/0001	A.2.a - Administrative change - Change in the (invented) name of the medicinal product for CAPs	27/08/2013	26/08/2014	SmPC, Labelling and PL	