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
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 -	19/11/2018		Annex II and PL	

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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	Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
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 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	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 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.	14/09/2017	n/a		

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
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 authorisation, including the RMP - Other variation	13/09/2016	24/05/2017	SmPC, Annex 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 • 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)	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 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

	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				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	Periodic Safety Update EU Single assessment -	24/09/2015	19/11/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending

/201502	pomalidomide				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	17/12/2014	n/a		

	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				
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	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

	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 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				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 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	