Revlimid

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/0129/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the	04/01/2024		Annex II	

[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).

	obligations and conditions of a marketing authorisation, including the RMP - Other variation				
II/0126	Submission of the final report from study CC-5013-MDS-010 listed as an obligation in the Annex II of the Product Information. This is a prospective non-interventional post-authorisation safety study (PASS), designed as a disease registry of patients with transfusion dependent IPSS low or intermediate-1-risk myelodysplastic syndromes (MDS) and isolated del(5q). Section 4.8 of the SmPC is updated with the adverse drug reaction of anaemia in patients with myelodysplastic syndromes. Section D of the Annex II and the RMP (version 39.1) are updated accordingly. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	28/09/2023		SmPC and Annex II	
PSUSA/1838/202212	Periodic Safety Update EU Single assessment - lenalidomide	31/08/2023	n/a		PRAC Recommendation - maintenance
IA/0128	A.7 - Administrative change - Deletion of manufacturing sites	31/07/2023	n/a		
II/0123	Update of section 4.4 of the SmPC, Annex IID and Article 127a and the tools/documents included in the	08/06/2023	26/07/2023	SmPC, Annex II and PL	

	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 MAH is also taking the opportunity to update the RMP with PASS Protocol milestones. The updated RMP version 38.2 was provided. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IA/0127	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	11/07/2023	n/a		
II/0124	Update of section 5.1 of the SmPC in order to update 5-year Overall Survival data following the assessment of procedure II/107 based on study CC-5013-NHL-007, A Phase 3, Double-Blind Randomized Study To Compare The Efficacy And Safety Of Rituximab Plus Lenalidomide (Cc-5013) Versus	09/02/2023	26/07/2023	SmPC	

	Rituximab Plus Placebo In Subjects With Relapsed/Refractory Indolent Lymphoma. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0122	Please refer to the Recommendations section above C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2022	14/10/2022	SmPC and PL	SmPC new text Section 4.2 • Patients with renal impairment The table for Follicular lymphoma patients is updated to also reflect dose adjustment for those with severe renal impairment and end of stage renal disease Follicular lymphoma Renal function (CLcr) Dose adjustment (days 1 to 21 of repeated 28 day cycles) Severe renal impairment (CLcr < 30 mL/min, not requiring dialysis) 5 mg once daily End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis) 5 mg once daily. On dialysis days, the dose should be administered following dialysis. Section 4.4 Additional precautions … Patients should not donate blood, semen or sperm during treatment (including during dose interruptions) and for at

					least 7 days following discontinuation of lenalidomide. For more information, please refer to the Summary of Product Characteristics.
IB/0120	C.I.3.a - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Implementation of wording agreed by the competent authority	21/12/2021	14/10/2022	Annex II	
IAIN/0121	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	09/12/2021	14/10/2022	Annex II and PL	
IA/0119	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)	22/09/2021	n/a		
PSUSA/1838/ 202012	Periodic Safety Update EU Single assessment - lenalidomide	22/07/2021	16/09/2021		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1838/202012.
IA/0118/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	09/08/2021	n/a		

T/0116	Transfer of Marketing Authorisation	30/10/2020	16/11/2020	SmPC, Labelling and PL	
PSUSA/1838/201912	Periodic Safety Update EU Single assessment - lenalidomide	23/07/2020	24/09/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1838/201912.
II/0112/G	This was an application for a group of variations. Group of variations including one type II to update sections 4.2, 4.4 and 4.8 of the SmPC and section 4 of the PL with anaphylactic reactions reported with a rare frequency following a safety review and 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. Section 4.4 of the SmPC and Annex IID have been updated regarding the educational materials, prescribing and dispensing restrictions in order to provide more clarity about the recommended maximum duration of treatment. Finally the MAH took the opportunity to make editorial changes throughout the product information. 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	30/04/2020	02/06/2020	SmPC, Annex II and PL	A Safety Topic Review was undertaken to evaluate reports of anaphylactic reactions in patients treated with lenalidomide. This was as a result of anaphylactic reactions with pomalidomide, a compound of the same class (immunomodulatory drugs) being identified as a potential safety signal during routine signal detection activities. The SmPC has been updated to include information on anaphylactic reactions in sections 4.2, 4.4 and 4.8 (with a rare frequency). Lenalidomide must be discontinued for angioedema, anaphylactic reaction, exfoliative or bullous rash, or if SJS, TEN or DRESS is suspected, and should not be resumed following discontinuation for these reactions. Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction depending on severity. 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 lenalidomide. 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 side effects has been updated accordingly. For more information, please refer to the Summary of Product Characteristics.
II/0107	Extension of indication to include Revlimid in combination with rituximab (anti-CD20 antibody) for the treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3a); as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated; the PL is updated in accordance. The RMP version 37.0 has also been agreed. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	14/11/2019	18/12/2019	SmPC and PL	Please refer to Scientific discussion Revlimid-H-C-717-II-0107.

IB/0114/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile 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	29/11/2019	n/a		
II/0110	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	31/10/2019	n/a		
PSUSA/1838/201812	Periodic Safety Update EU Single assessment - lenalidomide	05/09/2019	n/a		PRAC Recommendation - maintenance
IA/0113	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)	14/08/2019	n/a		
II/0102/G	This was an application for a group of variations. Extension of indication to include treatment with Revlimid in combination with bortezomib and dexamethasone of adult patients with previously untreated multiple myeloma who are not eligible for	28/03/2019	13/05/2019	SmPC, Labelling and PL	Please refer to the Scientific Discussion Revlimid-II-102/G

	transplant. As a consequence, the MAH submitted a request to add 7-capsule pack sizes for the 7.5 mg, 20 mg and 25 mg strengths of Revlimid (lenalidomide) to support the proposed posology and lenalidomide dose modification. Sections 4.1, 4.2, 4.4, 4.8, 5.1, 6.5 and 8 of the SmPC are updated; the Package Leaflet is updated in accordance. Additionally, minor editorial changes have been introduced throughout the PI and annex II key elements of the RMM have been updated to include information on timing of blood and semen donation in line with the SmPC section 4.4. The RMP (version 36.4) 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 C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0111	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	10/05/2019	n/a		

IA/0109	A.7 - Administrative change - Deletion of manufacturing sites	13/03/2019	13/05/2019	Annex II and PL	
IAIN/0106	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	11/02/2019	13/05/2019	Annex II	
IA/0105	B.I.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation	18/12/2018	n/a		
IAIN/0104/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 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	19/11/2018	13/05/2019	Annex II and PL	

IB/0103	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/11/2018	13/05/2019	SmPC and PL	
PSUSA/1838/ 201712	Periodic Safety Update EU Single assessment - lenalidomide	12/07/2018	n/a		PRAC Recommendation - maintenance
T/0101	Transfer of Marketing Authorisation	15/06/2018	29/06/2018	SmPC, Labelling and PL	
II/0098	Update of section 4.4 of the SmPC and of the Annex II key elements of the risk minimisation programme with information on prescription duration and to revise due dates of the PASS CC-5013-MDS-10 and 12; furthermore, the RMP version 35.1 has been revised in line with the updated Guideline on Good Pharmacovigilance Practices (GVP) Module V to propose the reclassification and/or renaming of known safety concerns associated with the use of lenalidomide. Consequently, Annex IID has been updated accordingly also to remove activities deemed not to belong to the risk minimisation measures. In addition, the labelling information related to the pregnancy prevention has been updated in line with other products in the class. Minor editorial changes have also been introduced throughout the PI. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated	17/05/2018	29/06/2018	SmPC, Annex II and Labelling	Prescriptions for women of childbearing potential can be for a maximum duration of 4 weeks, and prescriptions for all other patients can be for a maximum duration of 12 weeks. The following elements have been removed from the safety advice relevant to all patients included in the healthcare professional's educational kit: description and management of neutropenia and thrombocytopenia including incidence rates from clinical trials, description and management of cutaneous reactions, description and management of hypersensitivity and angioedema, description and management of thromboembolic risk including incidence rates from clinical trials and post-marketing experience, description and management of hepatic disorders, use in patients with renal failure and explanation of the risk of neuropathy with long term use. Similarly, the following elements were removed from the educational brochure for patients: that Revlimid may cause neutropenia and thrombocytopenia and the need for regular blood tests and that Revlimid may cause venous and arterial thromboembolism.

	by new additional data to be submitted by the MAH where significant assessment is required				
II/0097	Update of the SmPC section 4.8 to include solid organ transplant rejection as an adverse reaction (ADR) with the frequency not known in line with the Company Core Data Sheet (CCDS). The MAH also took the opportunity to further align the SmPC section 4.8 with the CCDS by adding the following ADRs reported as serious in some clinical trials: cellulitis, hypercalcaemia, and musculoskeletal and connective tissue pain and discomfort (including back pain). Minor editorial changes have been introduced throughout the PI. The Package leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/04/2018	29/06/2018	SmPC and PL	
IA/0099/G	This was an application for a group of variations. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method 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	27/03/2018	n/a		

	an obsolete parameter) 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.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.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				
IA/0096	A.7 - Administrative change - Deletion of manufacturing sites	07/12/2017	n/a		
II/0095	Submission of the final results of the observational category 3 post-authorisation safety study (Study CC-5013-PASS-001) in subjects treated with lenalidomide to further characterise the safety profile of lenalidomide plus dexamethasone in the treatment of relapsed and/or refractory multiple myeloma in a real-world setting. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/10/2017	n/a		

PSUSA/1838/201612	Periodic Safety Update EU Single assessment - lenalidomide	20/07/2017	18/09/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1838/201612.
IA/0094	A.7 - Administrative change - Deletion of manufacturing sites	07/04/2017	n/a		
II/0089/G	This was an application for a group of variations. Extension of Indication to add maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation; as a consequence, SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and Package Leaflet. A revised version of the RMP (version 34.0) has been approved as part of this application. Furthermore, the MAH introduced 7-day pack sizes for the 10 mg and 15 mg strengths with subsequent changes to the Product Information. 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.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one B.II.e.5.a.2 - Change in pack size of the finished	26/01/2017	23/02/2017	SmPC, Labelling and PL	Please refer to the Scientific Discussion Revlimid-II-89/G

	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				
R/0091	Renewal of the marketing authorisation.	15/12/2016	16/02/2017	SmPC, Annex II, Labelling and PL	
IB/0092/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	31/01/2017	18/09/2017	SmPC, Annex II, Labelling and PL	
IB/0090	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	26/10/2016	16/02/2017	Annex II	
PSUSA/1838/ 201512	Periodic Safety Update EU Single assessment - lenalidomide	21/07/2016	09/09/2016	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1838/201512.
IB/0088	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	14/07/2016	09/09/2016	SmPC, Annex II and PL	
II/0079	Extension of Indication to add treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL); as a consequence, SmPC sections 4.1, 4.2, 4.4, 4.7, 4.8, 5.1 and 5.2 have been	28/01/2016	08/07/2016	SmPC and PL	Please refer to the Scientific Discussion Revlimid-II-79

	updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and Package Leaflet. A revised version of the RMP (version 29.0) has been approved as part of this application. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0086	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	11/02/2016	n/a		
IA/0085	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	22/10/2015	n/a		
IA/0084	A.7 - Administrative change - Deletion of manufacturing sites	11/08/2015	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/1838/ 201412	Periodic Safety Update EU Single assessment - lenalidomide	09/07/2015	n/a		PRAC Recommendation - maintenance

II/0082	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	11/06/2015	01/06/2016	SmPC and PL	
IAIN/0081	C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	16/04/2015	01/06/2016	SmPC and PL	
X/0073/G	This was an application for a group of variations. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one Annex I_2.(c) Change or addition of a new strength/potency	18/12/2014	19/02/2015	SmPC, Labelling and PL	Please refer to Assessment Report: Revlimid-H-C-717-X-0073/G.
PSUV/0074	Periodic Safety Update	24/07/2014	30/09/2014		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0074.
IA/0078	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	25/09/2014	n/a		
II/0070	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	30/09/2014	SmPC and Labelling	
IA/0077	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold	05/05/2014	n/a		

	increase compared to the originally approved batch size				
IA/0075	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	16/04/2014	n/a		
II/0072	Update of sections 4.4 and 4.8 of the SmPC in order to add hyperthyroidism and leukocytoclastic vasculitis as adverse drug reactions (ADRs) further to a PRAC request made during the assessment of Revlimid PSUR 08. The MAH took this opportunity to include minor changes to sections 4.4, 4.5, 4.6, 4.8 and 5.1 of the SmPC based on previously approved wordings. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/02/2014	30/09/2014	SmPC and PL	The MAH submitted a variation application in order to add the adverse drug reactions 'hyperthyroidism' and 'leukocytoclastic vasculitis' to sections 4.4 and 4.8 of the SmPC further to a PRAC request made during the assessment of PSUR 08. The MAH took this opportunity to include minor editorial changes to the SmPC and Package Leaflet in order to improve the clarity of document.
IA/0071	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	16/12/2013	n/a		
II/0067/G	This was an application for a group of variations. Group of a type II and two type IA variations	21/11/2013	n/a		

	- B.II.d.1.e) to align the specification for related impurities with the ICH Q3A terminology and to widen the limit at release and at end of shelf life. The MAH also proposed to reclassify an impurity and tighten its specification limits for both release and shelf life. - B.II.d.1.c) to add a specification parameter for the appearance of the 2.5 and 7.5mg capsules, this change was already approved for the other authorised strengths. - B.II.d.1.d) to delete a non-significant criterion from the description of appearance of capsules. In addition minor editorial changes are being made to the specifications of the finished product. B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter				
PSUV/0069	Periodic Safety Update	19/09/2013	13/11/2013	SmPC and PL	Update of section 4.5 and 4.8 of the SmPC to add the adverse reaction rhabdomyolysis, especially when statins are combined with lenalidomide. Please refer to: Revlimid-H-C-717-PSUV-0069 EPAR -

					Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
IB/0068/G	This was an application for a group of variations. 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 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 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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	22/10/2013	n/a		
IA/0066/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished	15/07/2013	n/a		

	product formulation - Change that does not affect the product information				
IG/0310	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	01/07/2013	n/a		
II/0056	Extension of Indication to include patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate for Revlimid. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	25/04/2013	13/06/2013	SmPC, Annex II, Labelling and PL	The MAH applied for an extension of indication to include patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate for Revlimid. The variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.
IAIN/0064	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	04/06/2013	n/a		
IB/0061/G	This was an application for a group of variations. 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	19/04/2013	13/06/2013	SmPC, Labelling and PL	

IAIN/0063	B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	12/04/2013	n/a		
IG/0278	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/03/2013	n/a		
II/0060	Update of section 4.2 of the SmPC in order to propose 7.5 mg daily dosing as an alternative to 15 mg dosing every other day for patients with severe renal impairment (creatinine clearance [CLcr] < 30 mL/min, not requiring dialysis). Furthermore, the PI is being brought in line with the latest QRD template version 8 rev.2 for the update of the Annex II. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	13/12/2012	17/01/2013	SmPC and Annex II	In the present variation, dose adjustments recommendation for patients with severe renal impairment receiving lenalidomide were amended to propose, in countries where the 7.5 mg hard capsules are available, 7.5 mg daily dosing as an alternative to the current 15 mg dosing every other day, based on the results of simulation of concentration-time profile, which suggest that the steady-state daily AUC (2506 ng•h/mL) at 7.5 mg once daily in patients with severe renal impairment is similar to that at 25 mg once daily in patients with CLcr ≥ 50 mL/min (AUC = 2392 ng•h/mL).
II/0058	Update of sections 4.4 and 4.8 of the SmPC regarding lenalidomide-induced hepatotoxicity further to the request of the CHMP (PSUR 7 and FU2 006.1). The Package Leaflet has been udpated accordingly. Section 4.5 of the SmPC was also updated to include a caution with potent P-gp inhibitors, whereby their concomitant use should be avoided due to increased plasma levels and toxicity. Annex II of the Product Information was also	18/10/2012	19/11/2012	SmPC, Annex II and PL	Following the assessment of PSUR 07 and FUM 006.1, the CHMP requested a thorough analysis of risk factors that could induce and/or increase Lenalidomide hepatotoxicity as well as an analysis of the patients who resumed Revlimid at reduced dose (with full narratives and CIOMS). Further to this analysis, the MAH has updated sections 4.4 and 4.8 of the SmPC and section 4 of the Package Leaflet. In section 4.4, a warning regarding worsening or impairing renal function and regarding co-existing viral liver has been added. A warning regarding any other potential risk factor

	updated in Section CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT as to include the requirement to circulate the DHPC Letter to healthcare professionals in countries where Revlimid is already launched, informing them of the hepatic risk of the product. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				of lenalidomide-induced hepatotoxicity and a statement on reducing dose should be considered. Section 4.8 has been updated and the following adverse events have been added with frequency unknown (acute hepatic failure, mixed cholestatic and cytolytic hepatitis, cytolytic hepatitis, cholestatic hepatitis and hepatitis toxic) or uncommon (hepatic failure). In addition to this, Section 4.5 of the SmPC was updated to include a caution with potent P-gp inhibitors (cyclosporine, clarithromycin, itraconazole, ketoconazole, quinidine, verapamil), mentioning that the latter may give raise to an increase of its plasma levels and its toxicity, and suggesting the avoidance of their concomitant use, if possible. Annex II of the Product Information was also updated in Section CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT as to include the requirement to circulate the DHPC Letter to healthcare professionals in countries where Revlimid is already launched, informing them of the hepatic risk of the product.
X/0046/G	This was an application for a group of variations. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one Annex I_2.(c) Change or addition of a new strength/potency	21/06/2012	10/09/2012		Please refer to Assessment Report: Revlimid-H-C-717-X-0046/G.
IG/0168/G	This was an application for a group of variations.	24/05/2012	n/a		

	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV 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.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 C.I.9.f - Changes to an existing pharmacovigilance system as described in the DDPS - Deletion of topics covered by written procedure(s) describing pharmacovigilance activities C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities 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				
IA/0057/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	18/04/2012	n/a		

	changes to an approved test procedure				
R/0054	Renewal of the marketing authorisation.	16/02/2012	13/04/2012	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Revlimid remains positive, but considers that its safety profile is to be closely monitored for the following reasons: - Given the seriousness of the adverse events reported since the initial granting of the marketing authorisation of Revlimid and particularly with respect to the recent reports of second primary malignancies and severe lenalidomide-induced hepatoxicity, a careful monitoring of any newly emerging safety signals is recommended. The CHMP decided that the MAH should continue to submit yearly PSURs. Therefore, based upon the safety profile of Revlimid, which requires the submission of yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
IB/0055	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	03/02/2012	n/a		
A20/0048	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 09 March 2011 the opinion of the CHMP on measures necessary to ensure the safe and effective use of the above mentioned medicinal product further to an increased incidence of second primary malignancies observed in newly diagnosed multiple myeloma patients, and to review its impact on the benefit risk	22/09/2011	13/01/2012	SmPC, Annex II and PL	Please refer to Assessment Report: Revlimid-H-C-717-A20-0048

	balance of the currently approved indication.				
IA/0052	A.7 - Administrative change - Deletion of manufacturing sites	26/08/2011	n/a		
IG/0100/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV 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.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 C.I.9.f - Changes to an existing pharmacovigilance system as described in the DDPS - Deletion of topics covered by written procedure(s) describing pharmacovigilance activities C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities 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	23/08/2011	n/a		

	the pharmacovigilance system				
IA/0051/G	This was an application for a group of variations. 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 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 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 B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	04/07/2011	n/a	Annex II and PL	
IA/0050/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV 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.d - Changes to an existing pharmacovigilance	21/06/2011	n/a		

	system as described in the DDPS - Change in the safety database 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 C.I.9.f - Changes to an existing pharmacovigilance system as described in the DDPS - Deletion of topics covered by written procedure(s) describing pharmacovigilance activities C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities 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				
IA/0049	A.1 - Administrative change - Change in the name and/or address of the MAH	16/05/2011	n/a	SmPC, Labelling and PL	
IA/0047	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	23/02/2011	n/a		
II/0042/G	This was an application for a group of variations. Update of section 5.2 of the Summary of Product	16/12/2010	21/01/2011	SmPC and Annex II	In this variation application, the Marketing Authorisation Holder of Revlimid provided the results of a study conducted to assess the effect of food on the bioavailability

	Characteristics regarding the absorption of lenalidomide in both the fed and fasted state based on data from Phase I studies in healthy volunteers and a Phase II study in patients with multiple myeloma. Changes were also made regarding the metabolism and excretion of lenalidomide in both healthy volunteers and in patients with multiple myeloma. As a consequence, redundant text was deleted and minor corrections were also made. The Marketing Authorisation Holder also took the opportunity to update Annex II to delete the version number of the DDPS. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				of lenalidomide following a single oral dose in healthy male subjects and also reviewed all pharmacokinetic data available on lenalidomide. Consequently, the product information was updated with regard to information on absorption as follows: Lenalidomide is rapidly absorbed following oral administration in healthy volunteers, under fasting conditions, with maximum plasma concentrations occurring between 0.5 and 2 hours post-dose. In patients, as well as in healthy volunteers, the maximum concentration (Cmax) and area-under-the-concentration time curve (AUC) increase proportionally with increases in dose. Multiple dosing does not cause marked drug accumulation. In plasma, the relative exposures of the S- and R-enantiomers of lenalidomide are approximately 56% and 44%, respectively. Co-administration with a high-fat and high-calorie meal in healthy volunteers reduces the extent of absorption, resulting in an approximately 20% decrease in area under the concentration versus time curve (AUC) and 50% decrease in Cmax in plasma. However, in the pivotal multiple myeloma registration trials where the efficacy and safety were established for lenalidomide, the drug was administered without regard to food intake. Thus, lenalidomide can be administered with or without food. Information on the metabolism and excretion of lenalidomide was also updated to indicate the following: A majority of lenalidomide is eliminated through urinary excretion. The contribution of renal excretion to total

					clearance in subjects with normal renal function was 90%, with 4% of lenalidomide eliminated in faeces. Lenalidomide is poorly metabolized as 82% of the dose is excreted unchanged in urine. Hydroxy-lenalidomide and N-acetyl-lenalidomide represent 4.59% and 1.83% of the excreted dose, respectively. The renal cl
II/0041	Update of section 4.2 of the Summary of Product Characteristics (SmPC) and the Package Leaflet to clarify that Revlimid capsules should not be opened and that dose management in patients with renal impairment should be based upon individual patient treatment tolerance as well as update of section 4.9 of the SmPC with additional information relating to available experience with overdose with lenalidomide. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/10/2010	17/12/2010	SmPC and PL	In this application, the Marketing Authorisation Holder (MAH) to Revlimid (lenalidomide) proposed to update section 4.2 of the SmPC and the package leaflet to clarify that the capsules should not be opened. Section 4.2 of the SmPC was also updated to add the clarification that after initiation of lenalidomide therapy, subsequent lenalidomide dose modification in renally impaired patient should be based on individual patient treatment tolerance. Further to findings from two studies conducted on subjects who received daily doses of lenalidomide, which exceeded the 25 mg daily starting dose in the approved indication, the MAH also proposed to update section 4.9 of the SmPC. The section describes the fact that there are some data available to inform prescribers on experience with exposure to doses of lenalidomide at 150 mg and 400 mg.
II/0034	Update of section 4.8 of the Summary of Product Characteristics (SmPC) to bring it in line with the Company Core Data Sheet and the SmPC guideline. The Package leaflet has been updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-	21/10/2010	17/12/2010	SmPC and PL	Further to the supportive information provided, the CHMP agreed for section 4.8 of the SmPC to be substantially updated to bring it in line with the CCDS and the SmPC guideline. Table 1 in section 4.8b now lists the ADRs reported in clinical studies in patients with multiple myeloma treated with lenalidomide as both "all ADRs" and "grade 3-4 ADRs".

	clinical, clinical or pharmacovigilance data				Table 2 in section 4.8b lists the adverse drug reactions identified from post-marketing data in patients treated with lenalidomide. Description of selected adverse reactions has been included in section 4.8c in accordance with the SmPC guideline. The package leaflet has been updated accordingly.
II/0032	Update of section 4.4 of the Summary of Product Characteristics with respect to arterial thromboembolic events and risk of thromboembolic events, following the request of the CHMP in the assessment of PSUR 5. Annex II, Annex 127a and the package leaflet have been updated accordingly. The MAH has taken the opportunity to also update the Product Information to the latest QRD template, version 7.3.1, along with minor formatting corrections. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	23/09/2010	13/12/2010	SmPC, Annex II, Labelling and PL	In patients with multiple myeloma, the combination of lenalidomide and dexamethasone is associated with an increased risk of venous and thromboembolism (predominantly deep vein thrombosis, pulmonary embolism, myocardial infarction and cerebrovascular accident). A review of arterial thromboembolic events (ATEEs) in Celgene Pharmacovigilance database through 26 December 2009, presented a total of 493 medically confirmed reports of ATEE. The overall reporting rate for ATEEs was 0.5%. The review showed predominance of cardiac events (65.7%, mainly myocardial infarctions with 319 reports). A causal relationship between lenalidomide and ATEEs cannot be excluded. However, possible explanations and predisposing factors remain to be determined, and the mechanisms involved in the physiopathology of myocardial infarctions remain unknown. The use of thromboprophylaxis was not documented in the majority of patients with ATEEs (>60%) and venous TEEs (>80%) while risk factors were identified in most of the patients with medically confirmed thromboembolic event. Prophylactic antithrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors. If the patient experiences any thromboembolic events, treatment must be discontinued

					and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the lenalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of lenalidomide treatment. The product information has been updated accordingly.
IA/0044	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	01/12/2010	n/a		
IA/0045	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	30/11/2010	n/a		
II/0033	Update of sections 4.2 and 5.1 of the SmPC, with respect to data from ECOG E4A03 study, further to the request of the CHMP (FU2 022.2). The package leaflet has been updated accordingly. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	23/09/2010	25/10/2010	SmPC and PL	At the time of the granting of the initial marketing authorisation, the Marketing Authorisation Holder (MAH) made the commitment to provide additional information on the Extension of the ECOG E4A03 study "A Randomized Phase III Study of lenalidomide (CC-5013) plus Dexamethasone versus CC 5013 plus Low Dose Dexamethasone in Multiple Myeloma with Thalidomide plus Dexamethasone Salvage Therapy for Non-Responders" (FU2 022.2). This open-label, randomized, multicenter, Phase 3 study was conducted in 445 patients with newly diagnosed multiple myeloma; 222 patients were randomized to the lenalidomide/low dose dexamethasone arm, and 223 were randomized to the lenalidomide/standard dose

					dexamethasone arm. Patients randomized to the lenalidomide/standard dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus dexamethasone 40 mg/day on Days 1 to 4, 9 to 12, and 17 to 20 every 28 days for the first four cycles. Patients randomized to the lenalidomide/low dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus low dose dexamethasone 40 mg/day on Days 1, 8, 15, and 22 every 28 days. In the lenalidomide/low dose dexamethasone group, 20 patients (9.1%) underwent at least one dose interruption compared to 65 patients (29.3%) in the lenalidomide /standard dose dexamethasone arm. In a post-hoc analysis, lower mortality was observed in the lenalidomide /low dose dexamethasone arm 6.8% (15/220) compared to lenalidomide standard dose dexamethasone arm 19.3% (43/223), in the newly diagnosed multiple myeloma patient population, with a median follow up of 72.3 weeks. However with a longer follow-up, the difference in overall survival in favour of low dose dexamethasone tends to decrease. Considering that the patient population differs from the authorised indication, these results should be interpreted with caution. The product information has been updated further to the results of this study.
IA/0043	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	13/10/2010	n/a	Annex II and PL	

IA/0037/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV 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.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 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	06/07/2010	n/a	Annex II	
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	02/07/2010	n/a		
II/0027	Update of section 4.4 of the Summary of Product Characteristics (SmPC) to add a warning on myocardial infarction and to add it as a common adverse reaction in section 4.8 of the SmPC and in the package leaflet, further to the request of the CHMP in the assessment of the 4th Periodic Safety Update Report.	18/02/2010	23/03/2010	SmPC and PL	Following the assessment of the 4th Periodic Safety Update Report (PSUR), the CHMP requested the Marketing Authorisation Holder (MAH) to submit this type II variation application to update the product information with a warning on myocardial infarction and to add it as an adverse reaction. In this application, the MAH also provided a safety review of reports of myocardial infarction: a total

	Update of Summary of Product Characteristics and Package Leaflet				of 314 medically confirmed reports of myocardial infarction/ myocardial ischaemia with 318 adverse events were retrieved during the period covered from the first trial in man to 26 December 2008. As of 26 December, 2008, a total of 75 cases of myocardial infarction have been notified out of the 9308 patients exposed to lenalidomide throughout the clinical studies, i.e., a global incidence of 0.8%. However, a 1.98% incidence rate of myocardial infarction was observed in multiple myeloma patients. This frequency indicates that myocardial infarction is a common adverse reaction in multiple myeloma patients treated with Revlimid (lenalidomide). Consequently, the product information was updated to add a warning in section 4.4 of the SPC that "Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors. Consequently, patients with known risk factors should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (eg. smoking, hypertension, and hyperlipidaemia)." Myocardial infarction was added as a common adverse reaction in Section 4.8 of the SPC and in the Package Leaflet.
IB/0031	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	22/03/2010	n/a	SmPC and PL	

II/0028	Update of section 5.1 of the Summary of Product Characteristics (SPC) with the updated pooled follow-up analysis from Study CC-5013-MM-009 and Study CC-5013-MM-010, further to the request of the CHMP (FUM 020). Annex II was also updated in line with the latest QRD template (version 7.3) and the MAH also took the opportunity to update the version number of the Risk Management Plan with the latest agreed version 10.0. Update of Summary of Product Characteristics	19/11/2009	12/01/2010	SmPC and Annex II	At the time of the granting of the initial marketing authorisation, the Marketing Authorisation Holder (MAH) committed to provide updated time to tumour progression (TTP) and overall survival (OS) data from CC-5013-MM-009 and CC-5013-MM-010 clinical studies (FUM 020). The MAH submitted the results of the pooled extended follow-up analysis of studies CC-5013 MM-009 and CC-5013 MM-010 with cut-off dates of 23 July 2008 and 2 March 2008, respectively. Further to the assessment of this follow-up measure, the CHMP concluded that based on updated follow up data, TTP is still significantly higher in lenalidomide/dexamethasone treated patients than placebo/dexamethasone treated patients (HR=0.35; p<0.001). For OS, the benefit is less important but remains significant (HR=0.833; logrank p<0.045). The benefit-risk ratio of Revlimid remains positive. At the request of the CHMP, section 5.1 of the Summary of Product Characteristics (SPC) has been update in this type II variation to include the updated data from these clinical trials.
II/0029	Update of section 5.3 of the Summary of Product Characteristics (SPC) with the final results from the pilot embryo-foetal development Study CC-5013-TOX-004, at the request of the CHMP (FUM 014). Annex II & IV have been updated accordingly to reflect that the results are now final.	22/10/2009	08/01/2010	SmPC and Annex II	The final results from the pilot embryo-foetal development Study CC-5013-TOX-004 have now been included in section 5.3 of the SPC as follows: "An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses from 0.5

	Update of Summary of Product Characteristics				and up to 4 mg/kg/day. Findings from this study indicate that lenalidomide produced external malformations including non-patent anus and malformations of upper and lower extremities (bent, shortened, malformed, malrotated and/or absent part of the extremities, oligo and/or polydactyly) in the offspring of female monkeys who received the drug during pregnancy. Various visceral effects (discoloration, red foci at different organs, small colorless mass above atrio-ventricular valve, small gall bladder, malformed diaphragm) were also observed in single fetuses.
IB/0030	To change the storage conditions of the finished product IB_42_b_Change in storage conditions of the finished/diluted/reconstituted product	17/12/2009	n/a	SmPC, Labelling and PL	
II/0026	Update of sections 4.4, 4.6 and 5.2 of the SPC further to the results of study CC-5013-PK-008, conducted as a post-authorisation commitment to evaluate the transfer of lenalidomide in semen in healthy volunteers which confirmed the presence of lenalidomide in human semen (FU2 025.1). Annex II, the Package Leaflet and Annex IV have been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	24/09/2009	16/12/2009	SmPC, Annex II and PL	At the time of the initial marketing authorisation, the Marketing Authorisation Holder (MAH) committed to evaluate the risk for the foetus after paternal exposure. The results of a pharmacokinetic study to evaluate the transfer of lenalidomide in semen in healthy volunteers are now available. Results showed that lenalidomide is present in human semen (< 0.01% of the dose) after administration of 25 mg/day and the drug is undetectable in semen of a healthy subject 3 days after stopping the drug. The product information has been updated accordingly to reflect the available data.

					Based on this data, the warning that patients should not donate semen during therapy or for 1 week following discontinuation of lenalidomide was not considered warranted anymore. ''Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the drug in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception.''
II/0024	Update of DDPS (Pharmacovigilance)	24/09/2009	19/10/2009	Annex II	Update of the Detailed Description of the Pharmacovigilance System (DDPS) to version 6.0, in light of a reorganisation within Celgene's Drug Safety Department concerning the risk management activities. Consequently, Annex II has been updated with the new version number of the agreed DDPS.
II/0025	Further to the request of the CHMP during the assessment of the 3rd PSUR, the Marketing Authorisation Holder (MAH) applied to update section 4.4 of the Summary of Product Characteristics (SPC) to add warnings on allergic reactions (including hypersensitivity reactions and cross-allergy with thalidomide) and on severe skin reactions, and to update the warning concerning the use of	25/06/2009	07/08/2009	SmPC, Annex II and PL	Further to cases reported, Tumour Lysis Syndrome has been added as a rare adverse reaction reported during the post-marketing experience in section 4.8 of the Summary of Product Characteristics (SPC) and in the Package Leaflet. A warning on allergic reactions (including hypersensitivity reactions and cross-allergy with thalidomide) and a warning on severe skin reactions have been added in section 4.4 of

	erythropoietic agents with the currently approved threshold of Hb target (i.e 12 g/dl), and section 4.8 to add hypersensitvity reactions and Tumour Lysis Syndrome as rare adverse reactions. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the version number of the RMP in Annex II with the latest agreed version 9.0. Update of Summary of Product Characteristics and Package Leaflet				the SPC as follows: Allergic Reactions Cases of allergic reaction/hypersensitivity reactions have been reported (see section 4.8). Patients who had previous allergic reactions while treated with thalidomide should be monitored closely, as a possible cross-reaction between lenalidomide and thalidomide has been reported in the literature. Severe skin reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. Lenalidomide must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions. Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction depending on severity. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide. Hypersensitvity reaction has been added as a rare adverse reaction in section 4.8 of the SPC. In section 4.4 of the SPC, the warning concerning the use of erythropoietic agents has been updated with the currently validated threshold of Hb target (i.e 12 g/dl).
II/0023	Change in the specifications of the active substance lenalidomide based on the increase knowledge of the manufacturing process, in-process and release data on commercial batches and stability results. Update of or change(s) to the pharmaceutical documentation	23/07/2009	29/07/2009		

II/0014	Update of section 4.8 of the SPC to add the adverse events Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis and Angioedema reported during the post-marketing period, and of section 4.4 and 4.8 of the SPC in order to include haemorrhagic potential related to concomitant antithrombotic treatment and haemorragic adverse reactions, further to the request from the CHMP following the assessment of the 2nd PSUR. The Package Leaflet is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	22/01/2009	24/02/2009	SmPC and PL	Further to the request from the CHMP in the assessment of the 2nd PSUR, the Marketing Authorisation Holder (MAH) conducted a safety review to evaluate the reports of several adverse events reported. Stevens Johnson Syndrome and Toxic Epidermal Necrolysis Stevens-Johnson Syndrome among patients receiving lenalidomide, retrieved a total of 13 SJS case reports (2 reports from clinical trials, 11 post-marketing reports received from healthcare professionals). In addition, a single report of Toxic Epidermal Necrolysis was reported. Overall, taking into account the potential causal relationship between Stevens-Johnson Syndrome occurrence and Lenalidomide (compatible time to onset, biopsy confirming diagnosis of SJS in one case, and evolution), the low but non negligible reporting rate (0.03%), and the seriousness of the pathology, the CHMP considered the MAH's proposal to add Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in section 4.8 of the SPC and in the Package Leaflet as a rare adverse event. Angioedema After reviewing data from clinical trials, post-marketing and literature, a total of 161 cases have been retrieved and analysed by the MAH. There were two reports of angioedema with positive re-challenges. Despite an unclear temporal relationship of lenalidomide to angioedema, clinicians should exercise caution when prescribing lenalidomide for patients who have had a history of hypersensitivity adverse reactions, specifically to thalidomide. Clearly, once angioedema has been identified, the risks and benefits of lenalidomide therapy should be considered. Therefore, angioedema was added in section 4.8 of the SPC and in the Package Leaflet as an uncommon

					adverse event. Haemorragic disorders Based on the review of all adverse events of haemorrhage reported during clinical trials and post-marketing experience and from the literature, the CHMP considered that there is an increased risk of haemorrhage among lenalidomide patients on anticoagulants, and t
IB/0020	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	23/01/2009	n/a	SmPC	
IA/0022	IA_05_Change in the name and/or address of a manufacturer of the finished product	19/01/2009	n/a		
IA/0021	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	19/01/2009	n/a		
II/0017	Update of Summary of Product Characteristics	20/11/2008	22/12/2008	SmPC	The scope of this variation is to update the section 4.2 of the SPC in line with the outcome of FUM 019 (dose schedule in renal impairment). In this same section 4.2, for the sake of clarity, the MAH also proposes to amend the table that describes the dose adjustment for patients who are affected by neutropenia during treatment.
II/0015	Update of DDPS (Pharmacovigilance)	23/10/2008	20/11/2008	Annex II	Update of the Detailed Description of the Pharmacovigilance System (DDPS). Consequently, Annex II of the product information has been updated to include the latest version number (version 5.1) of the DDPS agreed by the CHMP.
II/0016	Update of the information on the interaction with oral contraceptives in section 4.5 further to the request of the CHMP following the assessment of the results of	25/09/2008	27/10/2008	SmPC	Update of the information on the interaction with oral contraceptives in section 4.5 further to the request of the CHMP following the assessment of the results of in vitro

	in vitro evaluation of Revlimid as an inducer of cytochrome P450 expression in cultured hepatocytes (FUM 018). The study indicates that lenalidomide up to 10 ?M CC-5013, twice daily for three consecutive days does not induce CYP1A2, 2B6, 2C9, 2C19 and CYP3A4/5 in cultured human hepatocytes. Update of Summary of Product Characteristics				evaluation of Revlimid as an inducer of cytochrome P450 expression in cultured hepatocytes (FUM 018). The study indicates that lenalidomide up to 10 ?M CC-5013, twice daily for three consecutive days does not induce CYP1A2, 2B6, 2C9, 2C19 and CYP3A4/5 in cultured human hepatocytes.
IA/0019	IA_05_Change in the name and/or address of a manufacturer of the finished product	14/10/2008	n/a		
IA/0018	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	09/09/2008	n/a		
II/0005	Update of the Detailed Description of the Pharmacovigilance System (DDPS). Consequently, Annex II of the product information has been updated to include the latest version number (version 5.1) of the DDPS agreed by the CHMP. Update of DDPS (Pharmacovigilance)	26/06/2008	22/08/2008	Annex II	The Detailed Description of the Pharmacovigilance System has been updated (version 4.1).
IA/0013	IA_01_Change in the name and/or address of the marketing authorisation holder	07/08/2008	n/a	SmPC, Labelling and PL	
II/0008	Update of sections 4.4, 4.6 and 5.3 of the SPC with regard to non-clinical safety findings of teratogenicity in monkeys, upon request from the CHMP. A new version of the EU RMP is also proposed to reflect these findings. Annex II, Labelling, Package Leaflet	30/05/2008	31/07/2008	SmPC, Annex II, Labelling and PL	Following a request from the CHMP, the Marketing Authorisation Holder applied to update sections sections 4.4, 4.6 and 5.3 of the SPC with the preliminary results of an ongoing study in monkeys. These preliminary results showed that lenalidomide produced malformations (short

	and Annex IV have been updated accordingly. Update of Summary of Product Characteristics, Labelling and Package Leaflet				limbs, bent digits, wrist and/or tail, supernumerary or absent digits) in the offspring of female monkeys who received the drug during pregnancy. Based on these data, the CHMP considered that lenalidomide is teratogenic in animals and is expected to be teratogenic in humans. The Product Information and Risk Management Plan of Revlimid have been updated to reflect these findings and conclusion.
II/0012	Update of or change(s) to the pharmaceutical documentation	24/07/2008	29/07/2008		
IB/0011	IB_33_Minor change in the manufacture of the finished product	30/06/2008	n/a		
IB/0010	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	30/06/2008	n/a		
IA/0009	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	21/05/2008	n/a		
IB/0007	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	29/04/2008	n/a		
IA/0006	IA_13_a_Change in test proc. for active substance - minor change	04/04/2008	n/a		

II/0002	Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/01/2008	18/03/2008	SmPC, Annex II, Labelling and PL	This type II variation concerns an update of section 4.4 of the SPC with a clarification on the interval between prescription and dispensing and a warning on potential Tumour Lysis Syndrome and sections 4.4 and 4.6 of the SPC with clarifications regarding pregnancy testing and information concerning female partners of male patients who become pregnant. The Package Leaflet has been updated accordingly. Further, the Marketing Authorisation Holder (MAH) takes the opportunity to implement minor changes to the annexes IIB and IV in line with the latest Risk Management Plan approved by the CHMP (version 6.0) and to make minor editorial changes to the SPC, labelling and Package Leaflet.
IB/0004	IB_17_a_Change in re-test period of the active substance	23/01/2008	n/a		
IA/0003	IA_01_Change in the name and/or address of the marketing authorisation holder	11/12/2007	n/a	SmPC, Labelling and PL	