EMA/526933/2020

Thalidomide Celgene

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
PSUSA/2919/ 201910	Periodic Safety Update EU Single assessment - thalidomide	30/04/2020	15/09/2020		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2919/201910.
II/0061/G	This was an application for a group of variations. Group of variations including one type II to update	30/04/2020	02/06/2020	SmPC, Annex II and PL	Anaphylactic reactions with pomalidomide, a compound of the same class as thalidomide, were identified to be a potential safety signal during routine signal detection

[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).

	sections 4.2, 4.4 and 4.8 of the SmPC and section 4 of the PL with anaphylactic reactions with a not known frequency following a safety review and a Type IB 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. 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				activities. As a result, a review of anaphylactic reactions in patients treated with thalidomide was undertaken. The SmPC has been updated to include information on anaphylactic reactions in sections 4.2, 4.4 and 4.8 (with a not known frequency). Patients should stop taking Thalidomide Celgene and see a doctor straight away if they notice any of the following serious side effects – allergic reactions such as a localised or generalised pruritic rash, angioedema and anaphylactic reaction (serious types of allergic reaction that may be manifested as hives, rashes, swelling of eyes, mouth or face, difficulty of breathing, or itching). 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. ection 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 and handling of the product. he 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.

IA/0065/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer	25/05/2020	n/a		

IA/0064	B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer	13/03/2020	n/a		
IA/0062/G	This was an application for a group of variations. 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 B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer	22/11/2019	n/a		
PSUSA/2919/201810	Periodic Safety Update EU Single assessment - thalidomide	29/05/2019	31/07/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2919/201810.
IA/0060	A.7 - Administrative change - Deletion of manufacturing sites	07/05/2019	31/07/2019	Annex II and PL	
II/0056	Update of the RMP version 19.2 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 thalidomide and to provide more detail in relation to the pregnancy	14/02/2019	31/07/2019	SmPC, Annex II and PL	Male patients should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of thalidomide. The educational healthcare professional kit in Annex II has been updated to remove the following risks: venous and arterial thromboembolic events, cardiovascular events, and

	prevention. Consequently, Annex IID, SmPC sections 4.4 and 4.6 and the PL have been updated accordingly. Minor editorial changes have been introduced in 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 by new additional data to be submitted by the MAH where significant assessment is required				bradycardia and syncope, peripheral neuropathy, severe skin reactions, and somnolence. For more information please refer to the Summary of Product Characteristics.
IAIN/0058	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	11/10/2018	31/07/2019	Annex II and PL	
T/0057	Transfer of Marketing Authorisation	30/07/2018	08/08/2018	SmPC, Labelling and PL	
PSUSA/2919/ 201710	Periodic Safety Update EU Single assessment - thalidomide	31/05/2018	30/07/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2919/201710.
R/0054	Renewal of the marketing authorisation.	14/12/2017	08/02/2018	SmPC, Annex II and PL	
IA/0053	A.7 - Administrative change - Deletion of manufacturing sites	29/06/2017	n/a		
PSUSA/2919/	Periodic Safety Update EU Single assessment -	05/05/2017	n/a		PRAC Recommendation - maintenance

201610	thalidomide				
IA/0052	A.7 - Administrative change - Deletion of manufacturing sites	24/04/2017	n/a		
II/0050	Submission of a final clinical study report for Study CC-2001-CP-001 together with the population pharmacokinetics (PK) meta-analysis CC-2001-MPK-001 and bioanalytical report CC-2001-CP-001-BA undertaken to evaluate thalidomide PK in multiple myeloma subjects in order to fulfil legally binding measure LEG 027.3. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/02/2017	n/a		
IB/0049	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	01/02/2017	08/02/2018	SmPC, Annex II, Labelling and PL	
IA/0048/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 A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of	07/10/2016	n/a		

	manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites				
PSUSA/2919/201510	Periodic Safety Update EU Single assessment - thalidomide	26/05/2016	15/07/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2919/201510.
IA/0047/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	29/06/2016	n/a		
IA/0046	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	19/05/2016	n/a		
II/0043	Update of sections 4.2 and 4.8 of the SmPC in order to add new dosing information for elderly patients (>75 years) with untreated multiple myeloma receiving thalidomide in combination with melphalan and prednisone (MPT). In addition the MAH is updating the posology with the recommended starting doses for melphalan and prednisone for	22/10/2015	19/11/2015	SmPC and PL	For patients >75 years of age, the thalidomide recommended starting dose is 100 mg per day. The initial dose of melphalan is reduced for elderly >75 years of age considering baseline bone marrow reserve and renal function. The melphalan recommended starting dose is 0.1 to 0.2 mg/kg daily according to bone marrow reserve along with a further 50% dose reduction for moderate (creatinine

	completeness. The Package Leaflet is being updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and Package Leaflet. A revised RMP version 17 was agreed during the procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				clearance: ≥ 30 but < 50 mL/minute) or severe (CrCl: < 30 mL/minute) renal insufficiency. The maximum daily melphalan dose is 20 mg in patients > 75 years of age. The adverse reaction profile reported in patients >75 years of age treated with thalidomide 100 mg once daily was similar to the adverse reaction profile observed in patients ≤75 years of age in patients treated with thalidomide 200 mg once daily. However, due to additional comorbidities and risk factors, patients with age >75 years are potentially at risk for a higher frequency of serious adverse reactions.
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/2919/ 201410	Periodic Safety Update EU Single assessment - thalidomide	07/05/2015	n/a		PRAC Recommendation - maintenance
II/0038/G	This was an application for a group of variations. Group of variations related to the introduction of a new manufacturing site for the active substance (thalidomide) including the following changes: – addition of an alternative manufacturer and release testing site of thalidomide with consequential changes to the manufacturing process at this site – addition of alternative testing sites of the active substance – changes to the specification parameters for starting materials and reagents used in the synthesis	26/06/2014	n/a		

	of the active substance – addition of a specification limits to specifications for intermediates and the active substance – change of the acceptance criteria in the specification specifications for intermediates and the active substance – replacement of the test procedures by an alternative test procedure for starting materials and reagents used in the synthesis of the active substance B.I.a.1.c - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions 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.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.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.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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.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.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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate 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.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.2.z - Change in test procedure for AS or				

	starting material/reagent/intermediate - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation				
IB/0041	To clarify the wording in the Package Leaflet for myocardial infarction and thromboembolic events and other minor editorial revisions and to update the description of the immediate packaging in Annex A in line with the Summary of Product Characteristics. In addition to update the Product Information to QRD v9.0. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/06/2014	27/05/2015	SmPC, Annex II and PL	
IA/0040	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	21/05/2014	n/a		
PSUV/0039	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
IA/0037/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.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	30/07/2013	n/a		

	the product information				
IG/0310	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	01/07/2013	n/a		
IA/0035/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.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	21/05/2013	n/a		
IG/0278	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/03/2013	n/a		
II/0033	Update of sections 4.2, 4.4 and 4.8 of the Summary of Product Characteristics following the assessment of EU PSUR 06 covering the reporting period from 09 October 2010 to 10 October 2011 with safety information regarding grade 3-4 neutropenia, grade 3-4 thrombocytopenia, haematological disorders and hepatic disorders. The Package leaflet is updated accordingly. The MAH also took the opportunity to include the date of latest renewal. C.I.3.b - Implementation of change(s) requested	21/02/2013	09/04/2013	SmPC and PL	Sections 4.2 and 4.4 of the SmPC have been amended to reflect that grade 3 and 4 neutropenia and thrombocytopenia have been reported in patients receiving thalidomide therapy. Sections 4.4 and 4.8 of the SmPC have been amended with regard to haemorrhagic disorders due to the potential seriousness of gastrointestinal haemorrhage and the possible increased incidence of such events in patients with existing risk factors, including concomitant use of anticoagulants, thrombocytopenia, concomitant use of known haematotoxic agents, and/or underlying disease complication. Section 4.4 and 4.8 of the

	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				SmPC have been updated with regard to hepatic disorders due to possible existing risk factors, such as pre-existing liver disorder and use of concomitant hepatotoxic medications, in thalidomide treated patients.
II/0032	Update of sections 4.4 and 4.8 of the SmPC to add a warning and information on acute myeloid leukaemia and myelodysplatic syndromes as second primary maligancies in patients treated with thalidomide, as reported in study CC-5013-MM- 020 and further to a safety review conducted by the MAH. The Package Leaflet is updated accordingly. The Annex II of the Product Information was also updated to include the requirement to circulate the DHPC in countries where Thalidomide Celgene is already launched, informing healthcare professionals of the risk of second primary malignancies with thalidomide. Finally, the PI is being brought in line with the latest QRD template version 8.3. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/02/2013	09/04/2013	SmPC, Annex II and PL	A statistically significant increase of acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS) has been observed in an ongoing clinical study in patients with previously untreated multiple myeloma (MM) receiving the combination of melphalan, prednisone, and thalidomide (MPT). The risk increases over time and was about 2% after two years and about 4% after three years. An increased incidence of second primary malignancies (SPM) has also been observed in patients with newly diagnosed MM receiving lenalidomide. Among invasive SPMs, cases of MDS/AML were observed in patients receiving lenalidomide in combination with melphalan or immediately following high dose melphalan and autologous stem cell transplantation. The benefit achieved with thalidomide and the risk of AML and MDS must be taken into account before initiating treatment with thalidomide in combination with melphalan and prednisone. Physicians should carefully evaluate patients before and during treatment using standard cancer screening and institute treatment as indicated.
R/0030	Renewal of the marketing authorisation.	18/10/2012	18/12/2012	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of Thalidomide Celgene continues to be adequately and sufficiently demonstrated and considers that the benefit/risk profile of this medicinal product continues to be

					favourable. The CHMP recommends the renewal of the Marketing Authorisation for Thalidomide Celgene, subject to the conditions and obligations as laid down in Annex II to the Opinion. The CHMP recommends that the renewal of the marketing authorisation be granted for a further 5 years. The MAH should submit one additional renewal application in 5 years time for the reasons laid out in Annex IV of the Opinion. The MAH is requested to submit yearly PSURs unless otherwise specified by the CHMP.
II/0027/G	This was an application for a group of variations. Group of variations relating to the change in the formulation of Thalidomide Celgene, including: - changes to the qualitative and quantitative composition of excipients; replacement of currently approved six excipients (microcrystalline cellulose, povidone, stearic acid, colloidal anhydrous silica, crospovidone and anhydrous lactose) with two excipients (pregelatinised starch and magnesium sterate), - change in the manufacturing process - minor changes to the finished product specification to update the acceptance criteria and test procedure for appearance - minor changes to the test procedure for assay and identity, related impurities, dissolution and content uniformity - change in the composition of the immediate packaging material to replace PCTFE/PE/PVC blisters with PCTFE/PVC blisters - increase of the finished product's shelf-life to	13/12/2012	09/04/2013	SmPC, Labelling and PL	

	60 months - update to the acceptance criteria for microbiological testing of capsule shells - addition of several manufacturing sites of the finished product (including testing sites). B.II.a.3.b.2 - Changes in the composition (excipients) of the finished product - Other excipients - Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the product B.II.b.3.b - Change in the manufacturing process of the finished product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) 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 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.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.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.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.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.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.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms 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.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation 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				
II/0028	Update of sections 4.4 and 4.8 of the SmPC to add a new warning and update the safety information regarding allergic reactions (angioedema/urticaria) further to a safety review conducted by the MAH. The Package Leaflet is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/07/2012	23/08/2012	SmPC and PL	The MAH conducted a review of cases of angioedema and urticarial. A total of 398 events within 367 cases were retrieved from the safety database with a cut-off 9 April 2010, thus giving an overall cumulative incidence of 0.12% (367/304,244). There were 10 medically confirmed reports of positive rechallenge (of those 6 were serious) which are suggestive of a causal relationship between the occurrence of these events and thalidomide exposure. Thalidomide should be discontinued if a skin rash occurs and only resumed following appropriate clinical evaluation. If angioedema occurs, use of thalidomide should not be resumed. The product information has been updated accordingly.
IA/0031/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used	27/07/2012	n/a		

	in the manufacture of the AS A.7 - Administrative change - Deletion of manufacturing sites 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				
IG/0168/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)	24/05/2012	n/a		

	to the DDPS that does not impact on the operation of the pharmacovigilance system				
IB/0025	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	07/12/2011	n/a		
II/0023	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) and the package leaflet with information on the risks of amenorrhoea, severe infections, atrioventricular block, atrial fibrillation, pancreatitis and convulsions further to the request of the CHMP during the assessment of the 5th Periodic Safety Update Report (PSUR). The MAH also took the opportunity to make a minor editorial change in the labelling. 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	20/10/2011	22/11/2011	SmPC, Labelling and PL	Further to the assessment of the 5th PSUR covering the period from 10 April 2010 to 9 October 2010 and cumulative reviews on atrioventricular block, atrial fibrillation and pancreatitis, the Marketing Authorisation Holder (MAH) was requested by the CHMP to submit a variation in order to update the Product Information of Thalidomide Celgene with regards to the risks of amenorrhoea, severe infections, atrioventricular block, atrial fibrillation, pancreatitis and convulsions. A warning was introduced in section 4.4 of the SmPC in order to inform prescribers that the use of thalidomide could be associated with menstrual disorders including amenorrhea. Amenorrhea during thalidomide therapy should be assumed to result from pregnancy, until it is medically confirmed that the patient is not pregnant. It was also added that patients should be monitored for severe infections including sepsis and septic shock as well as for atrioventricular block. Section 4.8 of the SmPC has been updated to include the following adverse reactions reported during the post-marketing experience: severe infections (e.g fatal sepsis including septic shock), convulsions, atrial fibrillation, atrioventricular block, menstrual disorders including amenorrhea and pancreatitis.

					The package leaflet has been updated accordingly.
IA/0024	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	08/11/2011	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 the pharmacovigilance system	23/08/2011	n/a		

IA/0022/G	This was an application for a group of variations. B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	22/08/2011	n/a		
IA/0020/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 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	21/06/2011	n/a		

	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/0019	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	07/06/2011	n/a	Annex II and PL	
IA/0018	A.1 - Administrative change - Change in the name and/or address of the MAH	04/05/2011	n/a	SmPC, Labelling and PL	
II/0017	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) with information on the risks of myocardial infarction and arterial thromboembolic events and update of section 4.8 of the SmPC with regards to the risk of worsening of Parkinson's disease symptoms further to the request of the CHMP in the assessment of the 4th PSUR. Annex II, Annex 127a and the Package Leaflet have 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	17/02/2011	18/04/2011	SmPC, Annex II and PL	Further to the assessments of the 4th Periodic Safety Update Report (PSUR) covering the period from 10 October 2009 to 9 April 2010 and cumulative reviews on myocardial infarction and thromboembolic events, the Marketing Authorisation Holder (MAH) was requested by the CHMP to submit a variation in order to update the Product Information of Thalidomide Celgene with regards to the risk of worsening of Parkinson's disease symptoms, the risk of myocardial ischaemia/infarction and the risk of arterial thromboembolic events (TEEs). Worsening of Parkinson's disease (PD) Reports of PD/worsening PD have been reported with thalidomide in the post-marketing experience. Overall, based on the currently available information, there is no evidence of causal relationship between thalidomide and occurrence of newly diagnosed PD. However, in patients

					with underlying PD, thalidomide may have an additive effect on PD symptoms, since thalidomide itself is known to induce tremor, abnormal coordination, depression and confusion, which are also, part of PD symptoms. Consequently, "worsening of Parkinson's disease symptoms" was added in the product information as an adverse reactions related to post-marketing experience with thalidomide. Myocardial infarction Myocardial infarction (MI) has been reported in patients receiving thalidomide, particularly in those with known risk factors. Patients with known risk factors for MI, including prior thrombosis, should be closely monitored and action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Consequently a warning to that effect has been added to the product information and "myocardial" was added as an adverse reactions related to post-marketing experience with thalidomide. Arterial thromboembolic events Venous TEEs (deep venous thrombosis and pulmonary embolism) were already known risks of thalidomide. At the request of the CHMP, a cumulative safety review of arterial TE
II/0015	Update of sections 4.4, 4.5 and 5.2 of the Summary of Product Characteristics with all relevant pharmacokinetics data on thalidomide collected from FU2 003.1 and FU2 003.2, as requested by the CHMP. The Marketing Authorisation Holder also took the opportunity to update Annex II with the deletion of the version number of the DDPS and with the	18/11/2010	20/12/2010	SmPC and Annex II	At the time of the granting of the initial marketing authorisation, the Marketing Authorisation Holder (MAH) made the commitment to provide data of the ongoing clinical trial OPTIMUM (FUM 003). Altogether, thalidomide PK data derive from 47 out of the 499 myeloma patients included in OPTIMUM study (THA PH EU 2005 CL 001) and PK population study which developed

	latest agreed version number of the RMP (version 10.0). C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				a PK model from mixed population (96 healthy subjects and 47 myeloma patients). Thalidomide is metabolised almost exclusively by non-enzymatic hydrolysis. Non-enzymatic hydrolysis suggests that the potential for drug-drug interactions with thalidomide is low. There is a linear relationship between body weight and estimated thalidomide clearance; in MM patients with body weight from 47-133kg, thalidomide clearance ranged from approximately 6-12 L/h, representing an increase in thalidomide clearance of 0.621 L/h per 10kg body weight increase. However, the distribution of thalidomide is not influenced by age, gender, renal function and blood chemistry variables, to any significant level. Studies conducted in healthy subjects and patients with multiple myeloma suggest that Thalidomide is not influenced to any significant extent by renal or hepatic function (see section 5.2). However, this has not formally been studied in patients with impaired renal or hepatic function; therefore patients with severe renal or hepatic impairment should be carefully monitored for any adverse effects. Sections 4.4, 4.5 and 5.2 of the Summary of Product Characteristics have been updated accordingly.
II/0014	Update of sections 4.8 of the Summary of Product Characteristics (SmPC) to add the adverse drug reactions pancytopenia, hearing loss, renal dysfunction and hypersensitivity, reported in the post-marketing experience, as requested by the CHMP in the assessment of the 3rd Periodic Safety Update Report. The Package Leaflet has been	21/10/2010	26/11/2010	SmPC, Annex II and PL	Within the assessment report for the 3rd Periodic Safety Update Report (PSUR), the Marketing Authorisation Holder (MAH) was requested by the CHMP to submit a variation in order to update the Summary of Product Characteristics (SmPC) of Thalidomide Celgene with regards to the risk of renal dysfunction and the ADRs of pancytopenia and hearing loss. The MAH was also requested to review the

	updated accordingly. In addition, the MAH took the opportunity to align the product information with the latest QRD template (version 7.3.1) and to include the version number of the latest agreed risk management plan in Annex II (version 9.0). 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				events of hypersensitivity reactions in order to update the product information. Pancytopenia Cytopenias have been observed at a very common frequency in trials where thalidomide was administered in combination with melphalan and prednisone. Anaemia, leucopenia and thrombocytopenia were already included in the Thalidomide Celgene EU SmPC. A cumulative search of the pharmacovigilance database retrieved a total of 266 reports of pancytopenia. Of these, 262 reports were excluded from the review. Only 4 well documented reports of pancytopenia were reviewed. Pancytopenia was reported in patients receiving thalidomide monotherapy. Analysis of these 4 reports concluded that chronological data including time to onset and positive dechallenge in the context of thalidomide monotherapy and absence of confounding factors, are highly suggestive with a possible relationship between pancytopenia and thalidomide. Hearing loss A cumulative safety review of events of hearing loss/deafness identified 131 reports. Fifty-four (54) of these were serious and 77 non serious. The time to event onset was suggestive of a relationship between thalidomide therapy and the events of hearing disorders. Indeed, the time to onset ranged from 10 days

					up to 1095 days with a median of 145 days. Data on dechallenge and rechallenge (reported for 21 patients) strengthen the possible relationship between the event and thalidomide therapy. Five literature articles reported hearing loss/deafness in patients receiving thalidomide. One of these described a sudden loss of hearing as a possible thalidomide-
IA/0016	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	14/10/2010	n/a	Annex II and PL	
IA/0013/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	08/07/2010	n/a	Annex II	

II/0011	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SPC) with information regarding the risk of tumour lysis syndrome (TLS) and to update section 4.8 of the SPC to add the adverse drug reactions febrile neutropenia and gastrointestinal perforations reported in the post-marketing experience, as requested by the CHMP further to the assessment of the 2nd Periodic Safety Update Report. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	18/02/2010	23/03/2010	SmPC and PL	At the request of the CHMP following the assessment of the 2nd Periodic Safety Update Report, section 4.8 of the SPC was updated to add the adverse drug reactions febrile neutropenia, gastrointestinal perforations and tumour lysis syndrome further to reports from the post-marketing experience. In addition, a warning was added in section 4.4 of the SPC to indicate that patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken. The Package Leaflet has been updated accordingly.
II/0010	Update of section 5.2 of the SPC with results of human mass balance study clarifying the route and fate of elimination of thalidomide, as requested by the CHMP following the assessment of FUM 002. Update of Summary of Product Characteristics	18/02/2010	23/03/2010	SmPC	At the time of the granting of the initial marketing authorisation, the Marketing Authorisation Holder (MAH) made the commitment to provide results of the human mass balance study clarifying route and fate of elimination of thalidomide (FUM 002). The MAH conducted a phase I trial: Mass balance, metabolism and pharmacokinetic study of 14C-labeled thalidomide in healthy male subjects following single oral dose administration. Within this study, clinical PK parameters determination and metabolite profiling and identification were conducted. In plasma, unchanged thalidomide represents 80% of the circulatory components. Unchanged thalidomide was a minor component (<3% of the dose) in urine. In addition to thalidomide, hydrolytic products N-(o-carboxybenzoyl)

					glutarimide and phthaloyl isoglutamine formed via non-enzymatic processes are also present in plasma and in majority in urine. Oxidative metabolism does not contribute significantly to the overall metabolism of thalidomide. Following a single oral dose of 400 mg of radio-labelled thalidomide, the total mean recovery was 93.6% of the administered dose by Day 8. The majority of the radioactive does was excreted within 48 hours following dose administration. The major route of excretion was via the urine (>90%) while faecal excretion was minor. Considering that pharmacologically active metabolites are eliminated via urine, patients with severe renal impairment should be carefully monitored for adverse reactions. Section 5.2 of the Summary of Product Characteristics has been updated accordingly.
IA/0012	IA_05_Change in the name and/or address of a manufacturer of the finished product	16/12/2009	n/a	Annex II and PL	
II/0007	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/0008	Update of Summary of Product Characteristics and Package Leaflet	23/07/2009	27/08/2009	SmPC and PL	The Marketing Authorisation Holder proposed a minor update section 4.4 of the Summary of Product Characteristics (SPC) to align the reference to the conditions of the Pregnancy Prevention Programme in line

					with the wording from sections 4.3 and 4.6 of the SPC. Minor editorial changes and changes to bring in line with QRD template were also proposed to the Package Leaflet.
II/0006	Update of section 4.2 of the SPC with regard to the recommended dose modifications due to peripheral neuropathy, further to the request of the CHMP following the review of available data to justify the extent of reduction of dose in case of thalidomide-related neuropathy. Update of Summary of Product Characteristics	22/01/2009	24/02/2009	SmPC	At the time of the granting of the initial marketing authorisation, no clinical data were provided by the Marketing Authorisation Holder (MAH) in order to justify the extent (50%) of reduction of dose in case of thalidomide-related neuropathy. Therefore, the MAH committed to provide a detailed review of all neuropathies observed in patients treated for multiple myeloma since the beginning of the named patients / cohort patients / compassionate use programme in the European Union (FUM 004). Based on the review of available data, the CHMP considered that the extent (%) of dose reduction was not justified. Therefore, the CHMP requested that the wording in section 4.2 of the SPC with regard to the extent of dose reduction "by up to 50%" should be deleted in the recommended dose modifications in cases of thalidomide-related neuropathy. In case of grade I neuropathy, however, dose reduction is not necessarily followed by improvement of symptoms.
II/0003	Update of DDPS (Pharmacovigilance)	23/10/2008	30/01/2009	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/0002	The MAH applied to add an additional manufacturer of the active substance (thalidomide). In addition an alternative manufacturing process for the active	20/11/2008	28/11/2008		

	substance was proposed. Change(s) to the manufacturing process for the active substance				
IB/0005	IB_02_Change in the name of the medicinal product	22/10/2008	n/a	SmPC, Annex II, Labelling and PL	
T/0004	Transfer of Marketing Authorisation from Pharmion Ltd. to Celgene. Transfer of Marketing Authorisation	03/10/2008	20/10/2008	SmPC, Labelling and PL	
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/07/2008	n/a	PL	