Bristol Myers Squibb™

Thalidomide

RISK MANAGEMENT PLAN

Version Number: 20.3

Data-lock Point for this RMP: 09-Oct-2021

Date of final sign off: 02-May-2023

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LIST OF ABBREVIATIONS

Term	Definition
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplantation
ASR	Age-standardised incidence rate
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
ATE	Arterial thromboembolism
ATU	Authorisations for use
AUC	Area under the curve
BMS	Bristol Myers Squibb
BMT	Bone marrow transplant
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CNS	Central nervous system
CSR	Clinical study report
CTD	Common Technical Document
CU	Compassionate use
Dex	Dexamethasone
DHPC	Direct Healthcare Professional Communication
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
E	Evaluation
EBV	Epstein-Barr Virus
EEA	European Economic Area
EMA	European Medicines Agency
ENL	Erythema nodosum leprosum
EPAR	European Public Assessment Report
EU	European Union
EU-RMP	European Union-Risk Management Plan
F	Female

Term	Definition
FCBP	Females of childbearing potential
FDA	Food and Drug Administration (US)
G-CSF	Granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
GVP	Good Pharmacovigilance Practices
Hb	Haemoglobin
HBeAg	Hepatitis B e antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCP	Healthcare professional
HDT/ASCT	High-dose therapy prior to autologous stem cell transplantation
hERG	Human ether-a-go-go-related gene
HHV	Human herpes virus
HLGT	High-Level Group Term
HLT	Higher Level Term
HMRN	Haematological Malignancy Research Network
IFM	Intergroupe Francophone du Myélome (French-Speaking Myeloma Group)
IIT	Investigator-initiated trial
IMiDs	Immunomodulatory drugs
INN	International Nonproprietary Name
INR	International normalised ratio
LMWH	Low-molecular-weight heparin
M	Male
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MM	Multiple myeloma
MP	Melphalan-prednisone
MPT	Melphalan-prednisone plus thalidomide
MTE	Mixed type thromboembolism
N/A	Not applicable
N/n	Number of patients
NA	Not available

Term	Definition
NCA(s)	National Competent Authority(ies)
NCI CTC	National Cancer Institute Common Toxicity Criteria
NDMM	Newly diagnosed multiple myeloma
NEC	Not elsewhere classified
NHL	Non-Hodgkin's lymphoma
NPP	Named Patient Programme
OR	Overall response
OS	Overall survival
PE	Pulmonary embolism
PL	Package Leaflet
PO	Orally
PPP	Pregnancy Prevention Programme
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred term
PTLD	Post-transplant lymphoproliferative disorders
QPPV	Qualified Person for Pharmacovigilance
R	Reporting
REMS™	Risk Evaluation and Mitigation Strategy
RMP	Risk Management Plan
ROW	Rest of world
RS	Relative survival
SAE	Serious adverse event
SCT	Stem cell transplantation
SD	Standard deviation
SEER	Surveillance, Epidemiology and End Results
SIR	Standardised incidence ratio
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System organ class
SPM	Second primary malignancies
S.T.E.P.S.®	System for Thalidomide Education and Prescribing Safety
STR	Safety topic review
TEE	Thromboembolic event
Thal	Thalidomide

Term	Definition
TNF	Tumour necrosis factor
TRMP	Thalidomide Risk Management Plan
TTP	Time to progression
UK	United Kingdom
ULN	Upper limit of normal
Unk	Unknown
US	United States
VAD	Vincristine, adriamycin and dexamethasone
VMP	Velcade (bortezomib)-melphalan-prednisone
VMPT	Velcade (bortezomib)-melphalan-prednisone-thalidomide
VTD	Velcade (bortezomib) plus thalidomide plus dexamethasone
VTE	Venous thromboembolism
WBC	White blood cell
WHO	World Health Organization
XPRT	Xanthine-guanine phosphoribosyl transferase

EU RISK MANAGEMENT PLAN (RMP) FOR THALIDOMIDE

RMP version to be assessed as part of this application:

Version Number: 20.3

Data-lock Point for this RMP: 09-Oct-2021

Date of Final Sign-off: 02-May-2023

Rationale for submitting an updated RMP:

- Updated the marketing authorization holder to Bristol Myers Squibb Company.
- Updated Annex 6 to align with GVP XVI and terminology between IMiDs.
- Updated to reflect data lock point 09-Oct-2021.

Summary of significant changes in this RMP:

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
Part II Safety Specification		
SI Epidemiology of the indication(s) and target population(s)	NA	V18.0/ 01-Feb-2017
SII Non-clinical part of the safety specification	NA	V18.0/ 01-Feb-2017
SIII Clinical trial exposure	NA	V18.0/ 01-Feb-2017
SIV Populations not studied in clinical trials	NA	V18.0/ 01-Feb-2017
SV Post-authorization experience	Update of Section 2.5 Post-authorization Experience to align with PBRER.	V20.3/ pending
SVI Additional EU requirements for the safety specification	NA	V18.0/ 01-Feb-2017
SVII Identified and potential risks	Administrative update to remove Table 2.7.2-1. Update of Table 2.7.3.1-1 with information from data lock point.	V20.3/ pending
SVIII Summary of the safety concerns	NA	V19.2/31-Jul-2019
Part III Pharmacovigilance Plan	Reintegration of Pregnancy Prevention Programme (PPP) implementation monitoring on a country-specific basis, and drug utilisation studies.	V20.3 / pending

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
Part IV Plan for post-authorization efficacy studies	NA	V18.0/ 01-Feb-2017
Part V Risk Minimisation Measures	Reintegration of PPP implementation monitoring on a country-specific basis, and drug utilisation studies as additional pharmacovigilance activities.	V20.3 / pending
Part VI Summary of the Risk Management Plan	Updated to reflect changes in the RMP.	V20.3 / pending
Part VII Annexes		
ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	Updated	V19.2/ 31-Jul-2019
ANNEX 3 Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan	NA	V18.0/ 01-Feb-2017
ANNEX 4 Specific adverse drug reaction follow-up forms	Updated follow up forms with BMS name.	V20.3 /pending
ANNEX 5 Protocols for proposed and on-going studies in RMP Part IV	NA	V18.0/ 01-Feb-2017
ANNEX 6 Details of proposed additional risk minimisation activities	Updated to align with GVP XVI and terminology between IMiDs and Annex IID of the SmPC.	V20.3 / pending
ANNEX 7 Other supporting data	NA	V18.0/ 01-Feb-2017
ANNEX 8 Summary of changes to the risk management plan over time	Updated to reflect changes in the RMP.	V20.3 / pending

Other RMP versions under evaluation:

RMP Version Number	Submitted on	Procedure Number
None		

Details of the currently approved RMP:

Version number: 19.2

Approved with procedure: EMEA/H/C/000823/IB/0049

Date of approval (opinion date): 31-Jul-2019

EU RMP Contact Person: Priv. Doz. Dr. Stefan Kaehler, EU QPPV

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

1 PART 1: PRODUCT OVERVIEW

Table 1-1: Product Details

Active substance(s) (INN or common name)	Thalidomide
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressive agent L04AX 02
Marketing Authorisation	Bristol-Myers Squibb Pharma EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Thalidomide BMS 50 mg hard capsules
Marketing authorization procedure	Centralised Procedure – European Medicines Agency (EMA); Procedure Number: EMEA H/C/000823
Brief description of the product	Chemical class: Thalidomide is known by the chemical name of α (N phthalimido) glutarimide. Summary of mode of action and important information about its composition: Thalidomide has anti-angiogenic, anti-inflammatory, and immunomodulatory properties.
Hyperlink to the Product Information	Refer to proposed PI

Table 1-1: Product Details

Indication(s) in the EEA	**Current:** Thalidomide BMS in combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma (MM), aged ≥ 65 years or ineligible for high-dose chemotherapy. Thalidomide BMS is prescribed and dispensed according to the Thalidomide BMS PPP. **Proposed:** Not applicable.
Dosage in the EEA	**Current:** 200 mg/day, oral for patients ≤ 75 years of age 100 mg/day, oral for patients > 75 years of age **Proposed:** Not applicable.
Pharmaceutical form (s) and strength(s)	**Current:** Hard capsule, 50 mg **Proposed:** Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No

2 PART II: SAFETY SPECIFICATION

2.1 Epidemiology of the Indication(s) and Target Population(s)

2.1.1 Incidence, Prevalence and Mortality and Demographic Profile of the Multiple Myeloma Population

The incidence, prevalence, mortality, and demographics of the population of patients with MM are summarised in Table 2.1.1-1.

Table 2.1.1-1: Epidemiologic Characteristics of Multiple Myeloma

Multiple Myeloma	
Incidence and Prevalence	MM accounts for about 10% to 18% of haematologic malignancies.[1,2] The prevalence of MM varies from country to country in the EU. Overall, the estimated prevalence of MM in the EU in 2018 ranges from 1.79 to 3.61 in 10,000 persons (data on file). In Europe, 38,900 new cases of MM and 24,300 deaths due to MM were estimated in 2012.[3] Crude and ASRs of MM in the population of the EU-28 states are 6.6 and 3.0 per 100,000, respectively, based upon estimates obtained from GLOBOCAN 2012 data.[3] The 1-year, 3-year, and 5-year number of persons with MM and prevalence proportions of MM (ages 15 years and older) in the EU-28 countries were 5.8 per 100,000 persons, 13.4 per 100,000 persons and 18.0 per 100,000 persons, respectively.[3]

Table 2.1.1-1: Epidemiologic Characteristics of Multiple Myeloma

Multiple Myeloma	
	Gains in survivorship associated with new therapies will increase the prevalence of MM.
Demographics of the population: age, gender, racial and/or ethnic origin	Multiple myeloma incidence rates among males and females in Europe rise with increasing age intervals: 0.0 (ages 0 to 14 years), 0.2 (ages 15 to 39 years), 1.3 (ages 40 to 44 years), 2.9 (ages 45 to 49 years), 5.2 (ages 50 to 54 years), 8.1 (ages 55 to 59 years), 12.3 (ages 60 to 64 years), 17.9 (ages 65 to 69 years), 24.6 (ages 70 to 74 years) and 31.0 (ages 75 years and older).[3] The ASR incidence of MM in men in the EU-28 countries is 3.7, based upon the diagnosis of MM in 18,043 men. MM accounted for 1.3% of all malignancies in men.[3] The ASR incidence of MM in women in the EU-28 countries is 2.5, based upon the diagnosis of MM in 15,599 women. MM accounts for 1.4% of all malignancies in women.[3] Analysing 18,824 MM registrations with ethnicity obtained by linkage to the English Hospital Episodes Statistics Database,[4] reported markedly higher incidence rates of MM in Black African men (ASR 8.6 per 100,000) and Black Caribbean men (8.3) relative to White men (3.7). Similar results were obtained with MM incidence rates in Black African women (5.8) and Black Caribbean women (5.7) compared to White women (2.4). This pattern is similar to that reported in the US, where incidence rates of MM are markedly higher in Black men compared to White men (15.9 versus 7.8 per 100,000) and in Black women compared to White women (11.4 versus 4.6 per 100,000, respectively.[5] Racial differences in rates were also observed in the US population.[6]
Risk factors for the disease	Age is the most important risk factor for MM, although race and gender are also important. While strong familial clustering of MM suggests that underlying genetic factors are important, findings from studies of lifestyle, dietary, occupational and environmental risk factors have been inconsistent.[7,6]
Main treatment options	In the EU, treatment options for MM include oral MP, and high-dose dexamethasone as a single agent or as part of combination therapy. In most European countries, high-dose melphalan plus ASCT became a standard first line treatment offered mainly to patients with NDMM aged < 65 years[8,9] and the oral MP regimen remained as a standard treatment for older patients aged ≥ 65 years with NDMM. Marketing authorisations in the EU for the use of the combinations of MPT and VMP as first line therapy for the ASCT-ineligible population were granted in Aug 2008. Since these approvals in 2008, the other EU marketing approvals granted in this same setting are bendamustine (2010) and lenalidomide (2015) for adult patients with previously untreated MM who are not eligible for transplant. Thalidomide is also used in multiple combinations with clinical benefit in patients with relapsed/refractory myeloma.[10]
Mortality and morbidity (natural history)	Crude and age-standardised mortality rates of MM in the EU-28 population are 4.0 and 1.6 per 100,000, respectively, based upon estimates obtained from GLOBOCAN 2012.[3] Within the EU-28 population, 20,462 men and women died

Table 2.1.1-1: Epidemiologic Characteristics of Multiple Myeloma

Multiple Myeloma	
	with MM in 2012. The cumulative mortality risk of MM (ages 0 to 74 years) is 0.17%. According to GLOBOCAN 2012 data, MM accounts for 1.2% of all deaths among persons with invasive malignancy in the European population.[3] Between 1989 and 2009, 1206 patients with MM were identified through the Modena Cancer Registry,[11] corresponding to periods of conventional therapy (1988 to 1996), high dose melphalan and autologous stem cell transplantation (ASCT; 1997 to 2005) and novel agents (2006 to 2009). Relative survival (RS) and overall survival (OS) improved over the years, with little change noted for patients ≥ 75 years. The survival of MM patients aged < 65 years and, in particular, 65 to 74 years improved over time, especially after 2006. The most recent data from the European Society for Bone and Marrow Transplantation registry (2006 to 2010) reported 5 year OS in MM transplant recipients as follows: 61.5% (< 40 years of age), 62.8% (40 to 49 years). 59.9% (50 to 59 years), 58.8% (60 to 64 years), 53.3% (65 to 69 years), 49.7% (≥ 70 years).[12] In a retrospective analysis of MM patients who received haematopoietic stem cell transplantation, median OS was 79.5 months in those < 60 years of age and 63.4 months in those ≥ 60 years of age.[13]
Important co-morbidities	Renal Impairment[14,15,16] Peripheral Neuropathy[17,18,19] Thromboembolic Events[20,21,22,23] Anaemia, leukopenia and infection[24,14,25] Secondary Primary Malignancies[26,27,28,29,30,31] Graft versus Host Disease[32,33] Bone diseases[34,35,36] • Gastrointestinal haemorrhage[37,38]

2.2 Nonclinical Part of the Safety Specification

Full details of the nonclinical safety data for thalidomide are presented in the Nonclinical Overview (MAA, Module 2, Section 2.4 Nonclinical Overview).

A summary of the nonclinical findings and their relevance to human usage is outlined in Table 2.2-1.

Table 2.2-1: Nonclinical Risks and Relevance to Human Use

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
Toxicity Studies:	

Table 2.2-1: Nonclinical Risks and Relevance to Human Use

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
• Reproductive and Developmental Toxicity See Nonclinical Overview and Nonclinical Summary, Sections 2.4 [MAA, Module 2, Vol. 3] and 2.6 [MAA, M2, Vol. 5]) Fertility In a fertility and general reproduction study in rabbits, testicular degeneration was observed in males at dosages of ≥ 30 mg/kg/day; however, no thalidomide-related adverse effects on fertility indices and reproduction were observed up to the highest dose of 100 mg/kg/day in female rabbits and 500 mg/kg/day in male rabbits (approximately 5- and 25-fold the maximum human dose of 400 mg, respectively, based upon BSA). Thalidomide was found in the semen in a dose-dependent manner. Embryo-foetal development Thalidomide is a known human and animal teratogen. A large amount of animal data on embryo-foetal development are available in the published literature. Nonclinical study CC-5013-TOX-004 was a pilot embryo-foetal development study of lenalidomide (CC-5013) administered by oral gavage to pregnant cynomolgus monkeys. Thalidomide was used as a positive control in this study. The study report was completed on 30 Mar 2009. In this study, administration of thalidomide at 15 mg/kg/day from gestation days 26 to 28 elicited an increase in intrauterine death (40%), decrease in mean placental weight and expected teratogenicity including findings such as shift of the preputium to the left in 1 foetus, and in 2 foetuses severe malformations such as oligo- and/or polydactyly, shortened, absent and/or flexed parts of the extremities, and correlating skeletal findings as known from the thalidomide syndrome in humans. Mean exposure (area under the curve $[AUC]_t$) in the thalidomide group at 15 mg/kg/day on gestation days 26 to 28 ranged from 51,870 to 59,270 ng•hr/mL. Given the well-known teratogenic potential for thalidomide, these results do not suggest any new safety finding for thalidomide. Pre- and postnatal development A peri- and postnatal toxicity study performed in rabbits with thalidomide resulted in abortions, increased stillbirths and decreased pup viability during lactation. Pups from mothers treated with thalidomide had increased abortions, reduced body weight gain, alterations in learning and memory, decreased fertility, and reduced pregnancy index. These effects were observed at dosages of	Teratogenicity is a well-documented toxicity of thalidomide. Extensive evidence from the literature and the Marketing Authorisation Holder (MAH)'s additional reproductive toxicity studies provide solid data on the detrimental reproductive effects of thalidomide (see CTD Section 2.4 [MAA, M2, Vol. 3, Nonclinical Overview]). However, considering thalidomide's well-established teratogenic potential and the MAH's controls on usage, the available data do not alter the safety assessment or prescription controls for thalidomide. Thalidomide must never be used by women who are pregnant or could become pregnant unless all the conditions of the Thalidomide BMS PPP are met. The conditions of the Thalidomide BMS PPP, including appropriate contraception measures, must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential (Sections 4.3, 4.4, and 4.6, SmPC). As thalidomide is found in semen, as a precaution all male patients taking thalidomide must use condoms during treatment, during dose interruption and for at least 7 days following discontinuation of treatment, and semen should not be donated during the same period (Section 4.4, SmPC). The MAH operates a pregnancy prevention and controlled access programme that is directed towards the safe prescribing and dispensing of the product in addition to a comprehensive education programme (as outlined in the key elements of Annex IID).

Table 2.2-1: Nonclinical Risks and Relevance to Human Use

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
≥ 30 mg/kg/day; a no-observed-effect level was not identified. Evidence in the literature concerning developmental effects in the offspring of thalidomide-treated male rodents and rabbits bred to nontreated females is inconclusive.[39,40,41]	
• Carcinogenicity and Genotoxicity Thalidomide is not genotoxic. Thalidomide did not induce reverse mutation in an Ames assay or forward mutation at the XPRT locus in Chinese hamster ovary cells. Thalidomide was not clastogenic in an in vivo mouse micronucleus assay at doses up to 5000 mg/kg administered intraperitoneally. In 2-year studies in rodents, no evidence of carcinogenicity was observed at dosages of up to 300 mg/kg/day in mice and rats (exposures approximately 15, 13 and 39 times the estimated clinical AUC at the recommended starting dose in mice, male rats and female rats respectively).	The results of preclinical carcinogenicity and genotoxicity studies are outlined in Section 5.3 of the SmPC.
General Safety Pharmacology • Cardiovascular (including potential for QT interval prolongation) In a hERG assay, thalidomide produced a slight inhibition at 75 µg/mL and the degree of inhibition was insufficient to allow for an IC_{50} to be determined. In a dog isolated Purkinje fibre assay, it was determined that thalidomide is not expected to have direct effects on QRS complex duration or QT interval at concentrations up to approximately 12.5 µg/mL (5-fold higher than the maximum concentration of 2.3 µg/mL observed clinically following a therapeutic dose of 200 mg). In the BMS-sponsored 1-year oral toxicity study in dogs (Study 96583), no thalidomide-related electrocardiographic alterations were observed, even at the highest dose tested (1000 mg/kg/day), and there were no reports of QT prolongation in dogs.	A cumulative STR for the events of torsade de pointes/QT prolongation was conducted and submitted with Periodic Safety Update Report (PSUR) #8 (reporting period from 10 Oct 2012 through 09 Oct 2013). The review concluded that the majority of the reports did not provide sufficient information for medical review and noted multiple contributing factors, including cardiac morbidity, renal morbidity, postsurgical onset, PE/lung infiltrate and therapies that carry the identified risk of cardiac toxicity. There have been no reports to suggest a direct thalidomide-induced QT prolongation or torsade de pointes based on this review. These data support the clinical trial experience. No change to the Company Core Data Sheet and RMP is warranted at this time. Bradycardia and syncope have been reported that appear to be unrelated to QT prolongation. This risk of bradycardia and syncope is addressed in the SmPC (Sections 4.2, 4.4, 4.5, and 4.8). Patients should be monitored for syncope and bradycardia and dose reduction or discontinuation may be required. A Type II variation was submitted in Aug 2011 (CHMP opinion received 20 Oct 2011; Commission decision received on 22 Nov 2011) in order to add the event of

Table 2.2-1: Nonclinical Risks and Relevance to Human Use

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
	atrioventricular block to Sections 4.4 and 4.8 of the SmPC. The potential for an interaction with active substances known to induce torsade de pointes is addressed in the SmPC (Section 4.5).
• Nervous System The main secondary pharmacodynamic activity of thalidomide concerns its activity on the CNS. As thalidomide was initially approved as a sedative in Europe, its CNS properties are well known.[42,43,44] In the BMS-sponsored 13-week repeat-dose toxicity study, potential CNS depression (partially or completely closed eyelids) was noted in rats only during a thorough Functional Observational Battery evaluation after 90 days of treatment at an oral dose of 3000 mg/kg/day. Most published data reporting signs of CNS depression in laboratory animals were from studies using the intraperitoneal route, which may lead to higher drug plasma concentrations more rapidly than oral administration.	As thalidomide was initially approved as a sedative in Europe, the CNS properties of this product are well known. One of the most common CNS adverse side effects associated with thalidomide treatment is somnolence (Sections 4.2, 4.4, and 4.8 of SmPC). Patients should be instructed to avoid situations where somnolence may be a problem and to seek medical advice before taking other medicinal products known to cause somnolence (Sections 4.4 and 4.5, SmPC). If affected, patients should be instructed not to drive cars, use machinery or perform hazardous tasks while being treated with thalidomide (Sections 4.4 and 4.7, SmPC).
• Peripheral Neuropathy See Nonclinical Overview and Nonclinical Summary, Sections 2.4 [MAA, M2, Vol. 3] and 2.6 [MAA, M2, Vol. 5]) Thalidomide is known to induce peripheral sensory neuropathy, but the mechanism is unknown. Umapathi[45] has concluded that this may be due to thalidomide's inhibitory action on nuclear factor kappa B, which is necessary for nerve growth factor-mediated sensory neuron survival. In an effort to address this issue, detailed toxicity evaluations were performed as part of the company-sponsored GLP 13-week rat toxicity study (Study N002124A) and GLP, 1-year dog toxicity study (Study 96583). These studies failed to identify changes in rats and dogs consistent with peripheral neuropathy at doses up to 3000 mg/kg/day. Attempts to produce experimental neuropathy in laboratory animals had variable success, and good predictive animal models have not been identified for this condition.	Peripheral neuropathy, predominantly of the lower limbs, is a known clinical complication of thalidomide[46,44,47] and is documented in Section 4.8 of the SmPC. Based on a Kaplan-Meier analysis using the overall safety population of Study IFM 99-06, the median time to first neuropathy event for patients treated with MPT was 42.3 weeks (95% CI: 36.3, 47.1), whereas the median time to first neuropathy was not reached in the melphalan-prednisone (MP) group ($p < 0.0001$). A similar Kaplan-Meier analysis based on the number of patients who had a neuropathy event in Study THAL-MM-003 showed that the median overall time to first neuropathy event was 32.6 weeks (95% CI: 16.86, 45.43) in the thalidomide/dexamethasone group, whereas median time to first neuropathy was not reached in the placebo/dexamethasone group ($p < 0.0033$). Thalidomide should not be used in patients with clinical signs or symptoms of peripheral neuropathy unless the clinical benefits outweigh the risks (Section 4.4, SmPC). Clinical and neurological examinations are recommended in patients prior to starting thalidomide therapy, and routine monitoring carried out regularly during treatment (Section 4.4, SmPC). Dose reduction, interruption or discontinuation may be necessary depending on severity (Section 4.2, SmPC). Medicinal

Table 2.2-1: Nonclinical Risks and Relevance to Human Use

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
	products known to be associated with neuropathy should be used with caution in patients receiving thalidomide (Sections 4.4 and 4.5, SmPC).
Mechanisms for Drug Interactions	
Thalidomide has been shown to be a poor substrate for human hepatic microsomal P450 (MAA, M5, Vol. 11, N002168A Study Report). Thus, clinically important interactions between thalidomide and drugs that are metabolised by the cytochrome P450 enzyme system are unlikely.[48]	Concomitant ingestion of food delays absorption but has no effect on overall extent of absorption (MAA, M2, Vol. 6, Section 2.7.2 Summary of Clinical Pharmacology Studies [p. 41]). To reduce CNS effects, however, such as somnolence, the dose is normally taken at bedtime (SmPC, Section 4.2). In humans, thalidomide does not affect the metabolism of oral contraceptive hormones. Concomitant use of cytochrome P450 inducing agents such as glucocorticoids (including prednisone), rifampin, rifabutin, phenytoin and carbamazepine with hormonal contraceptive agents, however, may reduce the effectiveness of the contraception and the risk of breakthrough ovulation cannot be absolutely determined with any degree of certainty. Women of childbearing potential requiring treatment with one or more of these medicinal products must use another effective method of contraception. No interaction has been reported between digoxin and thalidomide or between warfarin and thalidomide in healthy volunteers. With respect to digoxin, it is not known whether the effect will be different in MM patients. Due to the increased risk of thrombosis in cancer patients, and a potentially accelerated metabolism of warfarin with corticosteroids, close monitoring of INR values is advised during thalidomide-prednisone combination treatment as well as during the first weeks after ending these treatments.
Other Toxicity-related Information or Data	
• Clinical Chemistry and Haematology Evaluations Decreased platelet counts were noted in the rat studies, however, little significance is given to these findings as they were sporadic (only occurred in the short-term studies) and species specific. The decrease in platelet counts in the repeat-dose 13-week rat toxicity study does appear to be related to thalidomide administration; however, this decrease did not result in clinical signs (Section 5.3, SmPC). Therefore, this finding appears to have little clinical importance.	The decrease in platelet counts observed in the rat studies has been reported in patients treated with thalidomide in combination with MP. The severity and rate of thrombocytopenia, however, were comparable to those observed in patients treated with MP alone (Section 4.8, SmPC). Thus, this finding appears to have little toxicological or clinical importance, in particular thrombocytopenia was not associated with any reported events of all forms of bleeding. However, as thrombocytopenia, including Grade 3 or 4 adverse reactions, has been reported in MM patients receiving MPT, patients should be monitored and dose delay, reduction or discontinuation may be required (Section 4.2, SmPC). Patients and physicians are advised to be observant for signs and symptoms of

Table 2.2-1: Nonclinical Risks and Relevance to Human Use

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
	bleeding (Section 4.4, SmPC), including gastrointestinal haemorrhage (Section 4.8, SmPC).
• Hypothyroidism The reporting of hypothyroidism as an adverse event (AE) in clinical trials of thalidomide prompted the inclusion of thyroid function testing in the company-sponsored 13-week rat toxicity study (Study N002124A) and 1-year dog study (Study 96583). Although no effects were observed in dogs, an apparently dose-dependent decrease in total and free thyroxine was observed in rats, especially females.	Symptomatic hypothyroidism is an uncommon adverse reaction associated with the use of thalidomide, and although subclinical hypothyroidism appears to be more common, this adverse reaction can be managed without any expected public health impact in term of severity, hospitalisation or fatalities. Hypothyroidism is documented in Sections 4.4 and 4.8 of the SmPC.

2.3 Clinical Trial Exposure

2.3.1 Clinical Trial Information

The clinical efficacy and safety of thalidomide in combination with melphalan and prednisone or dexamethasone in the treatment of previously untreated MM patients has been demonstrated in 3 studies. Data from these company-sponsored and cooperative group clinical trials form the basis for the use of thalidomide in the first line treatment of patients with untreated MM (Table 2.3.1-1).

Table 2.3.1-1: Clinical Trials in Untreated Patients with MM

Study	Population	Treatment	Primary Endpoint
Pivotal Study			
IFM 99-06 (pivotal)	First line N = 447 Stage I to III MM Age 65 to 75 or < 65 years and not suitable for HDT/ASCT	MPT vs MP vs VAD/peripheral blood SCT x 2 Thal: 200 mg/d up to 400 mg/d after 2 to 4 weeks (depending upon tolerability) twelve 6-week cycles	OS
Supportive Studies			
THAL-MM-003	First line N = 470 Age > 18 years Stage II, III MM	Thal/Dex vs Placebo/Dex over 28 days Thal: 50 mg/d escalated to 200 mg/d over 28 days Thal/Dex vs Dex	TTP
E1A00	Induction N = 200	Thal: 200 mg/d four 4-week cycles	OR

Table 2.3.1-1: Clinical Trials in Untreated Patients with MM

Study	Population	Treatment	Primary Endpoint
	Age > 18 years Stage I to III MM		

Notes: N = Number of patients (Efficacy population).
Source: MAA, M5, IFM 99-06 Study Report (Vol. 21 27), THAL-MM-003 Study Report (Vol. 28 41), and E1A00 Study Report (Vol. 42 43).

Patient populations exposed to thalidomide in the 3 clinical trials, as combination therapy are shown in Table 2.3.1-2.

The population of patients studied in the 3 clinical trials is representative of the MM patient population in general, in terms of age, baseline characteristics of the disease, duration and dose of treatment.

Table 2.3.1-2: Summary of Patient Populations with Untreated MM Exposed to Thalidomide as Combination Therapy

	IFM 99-06[a]		E1A00		THAL-MM-003	
	MP (N = 196)	**MPT (N = 125)**	**Thal/Dex (N = 99)**	**Dex Only (N = 101)**	**Thal/Dex (N = 235)**	**Placebo+Dex (N = 235)**
Planned	447		194		470	
Randomised/Analysed	447/447		207/200		470/470	
Treatment						
MPT or Thal/Dex	125		99		235	
MP or Dex	196		101		235	
VAD-SCT	126		-		-	
Age in Years						
Mean ± SD	69.7 ± 2.7	69.7 ± 2.9	63.9 ± 10.33	63.8 ± 10.59	64.0 ± 10.17	64.4 ± 9.57
Median	69.5	69.2	65.3	65.6	65.0	66.0
Range	65,75	64,76	38.7, 83.3	38.2, 82.7	39.0, 86.0	31.0, 84.0
Age Distribution in Years, n (%)						
< 70	112 (57.1)	75 (60.0)	N/A	N/A	N/A	N/A
≥ 70	84 (42.9)	50 (40.0)	N/A	N/A	N/A	N/A
< 65	2 (1.0)	1 (0.8)	49 (49.5)	48 (47.5)	109 (46.4)	108 (46.0)
≥ 65[b]	194 (99.0)	124 (99.2)	50 (50.5)	53 (52.5)	126 (53.6)	127 (54.0)
Gender, n (%)						
M	109 (55.6)	63 (50.4)	50 (50.5)	60 (59.4)	118 (50.2)	120 (51.1)
F	87 (44.4)	62 (49.6)	49 (49.5)	40 (39.6)	117 (49.8)	115 (48.9)

Table 2.3.1-2: Summary of Patient Populations with Untreated MM Exposed to Thalidomide as Combination Therapy (Continued)

	IFM 99-06[c]		E1A00		THAL-MM-003	
	MP (N = 196)	MPT (N = 125)	Thal/Dex (N = 99)	Dex Only (N = 101)	Thal/Dex (N = 235)	Placebo+Dex (N = 235)
Race, n (%)						
Caucasian/White	194 (99.0)	124 (99.2)	87 (87.9)	87 (86.1)	224 (95.3)	221 (94.0)
Black	0	0	11 (11.1)	11 (11.0)	7 (3.0)	10 (4.3)
Other/Unknown	2 (1.0)	1 (0.8)	1 (1.0)	3 (3.0)	4 (1.7)	4 (1.7)
Thalidomide Treatment, Median (range)						
Daily dose (mg)	–	217.4 (75.3, 400.0)	196.4 (36.2, 200.0)	–	200 (50.0, 250.0)	–
Duration (months)	–	10.5 (0.4, 26.9)	3.7 (0.44, 18.3)	–	6.9 (0.16, 35.3)	–
Baseline Disease Stage, n (%)						
I	18 (9.2)	13 (10.4)	13 (13.1)	17 (16.8)	2 (0.9)	2 (0.9)
II	50 (25.6)	33 (26.4)	47 (47.5)	42 (41.6)	76 (32.3)	88 (37.4)
III	127 (65.1)	79 (63.2)	39 (39.4)	42 (41.6)	157 (66.8)	145 (61.7)

[a] Data based on the intent to treat population; includes 3 subjects in the MP group and 1 subject in the MPT group who discontinued before receiving study treatment.

[b] Two subjects in the MP group and 1 subject in the MPT group were aged < 65 years but were ineligible for high dose therapy.

Source: MAA, M5, IFM 99-06 Study Report (Vol. 21 to 27), THAL-MM-003 Study Report (Vol. 28 to 41), and E1A00 Study Report (Vol. 42 to 43).

2.3.2 Patient Exposure

2.3.2.1 Exposure to Thalidomide as Combination Therapy in the Pivotal Clinical Trials

The activity of thalidomide in the treatment of previously untreated patients with MM has been demonstrated in 3 clinical trials (N = 1124). Details of these patient populations are provided in Table 2.3.1-2. Exposure to thalidomide in the pivotal study (IFM 99-06) and in the registration clinical trials overall (IFM 99-06, THAL-MM-003 and E1A00) is provided by duration in Table 2.3.2.1-1, by dose in Table 2.3.2.1-2, by age group and gender in Table 2.3.2.1-3, by ethnic origin in Table 2.3.2.1-4, and by baseline disease stage in Table 2.3.2.1-5.

Table 2.3.2.1-1: Duration of Exposure to Thalidomide as a Combination Therapy

Thalidomide Exposure in Patients with Untreated MM	**IFM 99-06**	**Overall[(a)]**
	MPT (N = 124)	**MPT or Thal/Dex (N = 460)**
	Patient-years	**Patient-years**
Duration of Exposure		
Cumulative up to:		
1 month	10.1	37.3
3 months	28.4	102.0
6 months	52.5	170.6
12 months	87.9	260.1
24 months	106.1	317.7
36 months	106.4	319.9
Median Duration (Range)		
Duration (months)	10.67 (0.49, 26.78)	5.82 (0.16, 35.20)

Duration of exposure in months is calculated as [(date of last dose – date of first dose + 1) ÷ 30.4].
[(a)]Studies IFM 99-06, THAL-MM-003 and E1A00 combined.
Notes: Details of thalidomide treatment (dose and duration) are based on the safety population.
Source: MAA, M5, IFM 99-06 Study Report (Vol. 21 to 27), THAL-MM-003 Study Report (Vol. 28 to 41), and E1A00 Study Report (Vol. 42 to 43).

Table 2.3.2.1-2: Exposure to Thalidomide as a Combination Therapy by Dose

Thalidomide Exposure in Patients with Untreated MM	**IFM 99-06**	**Overall[a]**
	MPT (N = 124)	**MPT or Thal/Dex (N = 460)**
	Patient-years	**Patient-years**
Daily Dose		
50 mg	0.3	19.1

Table 2.3.2.1-2: Exposure to Thalidomide as a Combination Therapy by Dose

Thalidomide Exposure in Patients with Untreated MM	IFM 99-06	Overall[a]
	MPT (N = 124)	MPT or Thal/Dex (N = 460)
	Patient-years	Patient-years
100 mg	14.2	44.7
150 mg	0.0	1.9
200 mg	41.5	194.6
300 mg	3.8	3.8
400 mg	42.4	42.4
Median Dose (Range)		
Daily dose (mg)	202.15 (20.20, 400.00)	179.62 (20.20, 400.00)

[a] Studies IFM 99-06, THAL-MM-003 and E1A00 combined.
Notes: Details of thalidomide treatment (dose and duration) are based on the safety population.
Study Thal-MM-003 patient [redacted] had 8 days of thalidomide at 250 mg, which has been included in the 200 mg calculation of patient-years.
Source: MAA, M5, IFM 99-06 Study Report (Vol. 21 to 27), THAL-MM-003 Study Report (Vol. 28 to 41), and E1A00 Study Report (Vol. 42 to 43).

Table 2.3.2.1-3: Exposure to Thalidomide as a Combination Therapy by Age and Gender

Thalidomide Exposure in Patients with Untreated MM	IFM 99-06				Overall[a]			
	MPT (N = 124)				MPT or Thal/Dex (N = 460)			
	Patients n (%)		Patient-years		Patients n (%)		Patient-years	
Gender	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Age Group (Years)[b]								
< 70	36 (29.0)	38 (30.6)	34.3	30.0	157 (34.1)	144 (31.3)	110.7	101.8
≥ 70	26 (21.0)	24 (19.4)	21.5	20.6	75 (16.3)	84 (18.3)	48.0	59.4
< 65[c]	0 (0.0)	1 (0.8)	0.0	0.3	81 (17.6)	80 (17.4)	55.4	59.3
≥ 65[c]	62 (50.0)	61 (49.2)	55.8	50.3	151 (32.8)	148 (32.2)	103.3	102.0

[a] Studies IFM 99-06, THAL-MM-003 and E1A00 combined.

[b] Age at randomisation.

[c] Age groups of ≤ 65 and > 65 years in the E1A00 study.
Notes: Details of thalidomide treatment are based on the safety population. **Source:** MAA, M5, IFM 99-06 Study Report (Vol. 21 to 27), THAL-MM-003 Study Report (Vol. 28 to 41), and E1A00 Study Report (Vol. 42 to 43).

Table 2.3.2.1-4: Exposure to Thalidomide as a Combination Therapy by Ethnic Origin

Thalidomide Exposure in Patients with Untreated MM	IFM 99-06		Overall[a]	
	MPT (N = 124)		MPT or Thal/Dex (N = 460)	
	Patients n (%)	Patient-years	Patients n (%)	Patient-years
Ethnic Origin				
Caucasian/White	123 (99.2)	106.3	435 (94.6)	302.0
Black	0 (0.0)	0.0	18 (3.9)	13.5
Other/unknown	1 (0.8)	0.1	7 (1.5)	4.4

[a] Studies IFM 99-06, THAL-MM-003 and E1A00 combined.
Notes: Details of thalidomide treatment are based on the safety population.
Source: MAA, M5, IFM 99-06 Study Report (Vol. 21 to 27), THAL-MM-003 Study Report (Vol. 28 to 41), and E1A00 Study Report (Vol. 42 to 43).

Table 2.3.2.1-5: Exposure to Thalidomide as a Combination Therapy by Baseline Disease Stage

Thalidomide Exposure in Patients with Untreated MM	IFM 99-06		Overall[a]	
	MPT (N = 124)		MPT or Thal/Dex (N = 460)	
	Patients n (%)	Patient-years	Patients n (%)	Patient-years
Baseline Durie-Salmon Disease Stage				
I	13 (10.5)	9.5	29 (6.3)	16.2
II	33 (26.6)	27.3	155 (33.7)	94.7
III	78 (62.9)	69.6	276 (60.0)	209.0

[a] Studies IFM 99-06, THAL-MM-003 and E1A00 combined.
Notes: Details of thalidomide treatment are based on the safety population.
Source: MAA, M5, IFM 99-06 Study Report (Vol. 21 to 27), THAL-MM-003 Study Report (Vol. 28 to 41), and E1A00 Study Report (Vol. 42 to 43).

Analyses of exposure in special populations such as patients with hepatic, renal or cardiac impairment were not performed, as these patients were not recruited to the clinical trials.

2.3.2.2 Cumulative Patient Exposure in Clinical Trials

Cumulatively up to the DLP of 09 Oct 2021, approximately 21,205 patients have been treated with thalidomide in clinical trials, with 1973 in the BMS development programme worldwide and an estimated 18,121 in non-BMS-sponsored studies globally.

Cumulative exposure to thalidomide during BMS-sponsored studies is provided in Table 2.3.2.2-1. Exposure was based on populations defined by protocol or as estimated from the randomisation scheme for the study, if appropriate.

Table 2.3.2.2-1: Overall Cumulative Patient Exposure –BMS-sponsored Clinical Trials up to 09 Oct 2021

Treatment	Number of Patients Exposed
Thalidomide Exposures	
Thalidomide monotherapy	937
Thalidomide combination therapy[a]	1036
Total Thalidomide Exposure	1973
Other Treatment Arm Exposures[b]	
Active treatment	1845
Placebo/no treatment/best supportive care	60
Total Other Treatment Arm Exposures	1905
Total Exposure to Any Treatment Arm	3878

BMS-sponsored studies include THAL-MM-003, CC-5013-MM-020, THA-PH-INT-2005-CL-001 (OPTIMUM), THAL-MM-99-002, THAL-CRC-001, MAYO 98-80-13, UARK-98-003, E1A00, IFM 99-06, THAL-MDS-001, THA I EU 2004 BA 1, PK-001, PK-004, PK-006, PK-007, PK-005, PK-UK001, PK-UK008, PK-003, THAL PK 011, THAL-PK-012, GKTH-01, LA TH 03-01/P020242, LA/TH 98006, THA PH EU 2007, THAL BE 001, THAL-BE-01-001, THAL-BA-001, CC-2001-CP-001.

[a] Possible combination therapies included thalidomide + dexamethasone, melphalan/prednisone, digoxin (PK study) or warfarin (PK study).

[b] Other treatment arms included placebo/best supportive care/no treatment, lenalidomide/dexamethasone, dexamethasone, dexamethasone/placebo, melphalan/prednisone, or vincristine/cyclophosphamide/dexamethasone/G-CSF/melphalan.

Overall, 3878 patients have been exposed to any treatment arm during all BMS sponsored studies (29 studies) with a total of 1973 exposures to thalidomide (937 to monotherapy and 1036 to combination therapy). Based on studies with demographic information available in patients exposed to thalidomide (monotherapy or combination therapy), when race was collected, 73.8% were Caucasian, 5.6% were Asian, 4% were black, 2.3% were "other" race. Approximately 44.6% of thalidomide-treated patients were ≥ 65 years and 33.8% were between 18 and < 65 years.[49]

2.3.2.3 Other Clinical Trial Experience

Compassionate-use: Global compassionate-use exposures to thalidomide are included in the estimate of commercial exposure to thalidomide (see Section 2.5).

Noninterventional studies: Any exposures during other noninterventional studies (eg, market research studies) globally are included in the estimate of commercial exposures to thalidomide (see Section 2.5.

Non-BMS-sponsored studies: In other clinical trial experience, 18,121 patients have been exposed worldwide to thalidomide in non-BMS-sponsored studies, including 10,690 in the US, 6764 in the EEA, 235 in Australia, 220 in Canada and 212 in ROW. Further details are provided in Table 2.3.2.3-1.[50]

Table 2.3.2.3-1: Cumulative Subject Exposure in Non-BMS-sponsored Clinical Trials by Region and Indication up to 09-Oct-2021

Indication	US	Canada	UK	China	Japan	EEA[a]	Australia/ New Zealand	ROW	Total
MM	3197	220	3188	0	0	2554	141	187	9497
MDS	356	0	0	0	0	0	80	20	646
MDS/AML	172	0	0	0	0	0	0	5	177
Solid tumour[b]	4730	0	723	0	0	5	0	0	5458
Other indications[c]	2235	0	53	0	0	241	14	0	2543
Overall Total[d]	**10,690**	**220**	**3964**	**0**	**0**	**2800**	**235**	**212**	**18,121**

[a] Includes the 27 EU countries, Norway, Iceland, Liechtenstein.

[b] Solid tumours include: Brain Cancer, Breast Cancer, GI Cholangiocarcinoma, GI Colorectal Cancer, GI Liver Cancer, GI Peritoneal Cancer, GU Bladder Cancer, GU Kidney Cancer, GU Prostate Cancer, Gynecological Other, Gynecological Ovarian Cancer, Gynecological Uterine Other, Head and Neck Cancer, Lung Cancer SCLC, Lung Mesothelioma, Neuroendocrine Tumors, NSCLC, Pancreatic Cancer, Sarcoma Kaposi, Sarcoma Leiomyo, Sarcoma Other, Sarcoma Soft-tissue, Skin Melanoma, and Thyroid cancer.

[c] Other indications include: Acute Myeloid Leukemia, Amyloidosis, Amyotrophic Lateral Sclerosis, Angiodysplasia, Chronic Lymphocytic Leukemia, Chronic Obstructive Pulmonary Disease, Crohn's Disease, Cutaneous Lupus Erythematosus, Cutaneous T-Cell Lymphoma, Diffuse Large B-Cell Lymphoma, Fibrosis, Follicular Lymphoma, Graft versus Host disease, Hepatitis, Hereditary Hemorrhagic Telangiectasia, Interstitial Cystitis, Leukemia Other, Lymphoma Hodgkin, Lymphoma NHL, Lymphoma Other, Mantle Cell Lymphoma, MPD Other, Myelofibrosis, Other, Prurigo Nodularis, Psoriasis, Rheumatoid Arthritis, Sarcoidosis, Scleroderma, Sjogren syndrome, Systemic Lupus Erythematosus, Ulcerative Colitis, Uveitis, and Waldenstrom's Macroglobulinemia.

[d] Overall Total does not include exposure from Named Patient Programs, Compassionate Use Programs, noninterventional studies, or Global Health studies.

2.4 Populations Not Studied in Clinical Trials

2.4.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Pregnancy	Thalidomide is a known human teratogen that causes severe life threatening birth defects.	No	Thalidomide is contraindicated in women of childbearing potential unless all the conditions of the Thalidomide BMS PPP are met and in male and female patients unable to follow or comply with the required contraceptive measures, as outlined in the

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
			Thalidomide BMS PPP (SmPC, Sections 4.3, 4.4 and 4.6).
Lactation	Animal studies in rabbits have shown excretion of thalidomide in breast milk, although it is unknown if this occurs in humans. Consequently, lactating women were excluded from enrolling into the clinical trials.	No	Section 4.6 of the SmPC recommends that female patients must not breastfeed when taking thalidomide, as it is not known if thalidomide passes into human milk.
Women of childbearing potential, except when all conditions of pregnancy prevention have been met	Thalidomide is a known human teratogen that causes severe life threatening birth defects.	No	Treatment with thalidomide is contraindicated in women of childbearing potential unless all the conditions of the Thalidomide BMS PPP are met (SmPC Section 4.3).
Patients unable to follow or comply with the required contraceptive measures	Thalidomide is a known human teratogen that causes severe life threatening birth defects.	No	Treatment with thalidomide is contraindicated in patients unable to follow or comply with the required contraceptive measures (SmPC Section 4.3).
Hypersensitivity to the active substance or to any of the excipients	To protect patient safety by ensuring that patients with known hypersensitivity to the medicinal product were not included in the clinical trials.	No	Treatment with thalidomide is contraindicated in patients who have hypersensitivity to thalidomide or to any of its excipients (SmPC Section 4.3).
Peripheral Neuropathy	Many of the chemotherapies used to treat MM (vincristine, platinum containing agents, thalidomide, bortezomib) can cause or worsen existing peripheral neuropathy.[51,52] This could influence the interpretation of the study data.	No	Section 4.2 of the SmPC states that patients should be monitored for peripheral neuropathy and provides dose modifications if peripheral neuropathy occurs. Warnings and precautions regarding the possibility of developing peripheral neuropathy when taking thalidomide are outlined in Section 4.4 of the SmPC. Peripheral neuropathy is also listed as an undesirable effect in Section 4.8 of the SmPC.
Renal Impairment	Patients excluded for safety reasons.	No	Section 4.4 of the SmPC states that patients with severe renal impairment

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
			should be carefully monitored for any AEs during thalidomide treatment. Data from patients with end-stage renal disease suggest no impact of kidney function on thalidomide pharmacokinetics (SmPC, Section 5.2). No dose adjustments for patients with renal impairment are required (SmPC, Section 4.2).
Hepatic Function	Patients excluded for safety reasons.	No	Section 4.4 of the SmPC states that patients with severe hepatic impairment should be carefully monitored for any AEs during thalidomide treatment. Studies conducted in healthy subjects and patients with MM suggest that thalidomide is not influenced to any significant extent by hepatic function (SmPC, Section 5.2). No dose adjustments for patients with hepatic impairment are required (SmPC, Section 4.2).
Infection	Specified primarily due to the use of chemotherapy and corticosteroids in comparator regimens. Such concomitant diseases could influence the interpretation of the study data.	No	Severe infections (sepsis, septic shock and viral reactivation of hepatitis B) is included as an important identified risk in the EU-RMP. This risk is adequately addressed through the risk minimisation and pharmacovigilance measures presented in Part V and Part III of the EU-RMP .
Haematology (eg, Hb < 7 g/dL, ANC < 1000 cells/mm^3 [1.0 x 109/L], platelet count < 50,000/mm^3 [50.0 x 10^9/L])	Specified primarily due to the use of chemotherapy and corticosteroids in comparator regimens.	No	Guidelines for dose adjustment for patients with neutropenia and thrombocytopenia are presented in Section 4.2 of the SmPC and warnings and precautions regarding the monitoring of patients treated with thalidomide for signs of haematological disorders are presented in Section 4.4 of the SmPC. Neutropenia, anaemia and thrombocytopenia are listed as ADRs and discussed in Section 4.8 of the SmPC.
Malignancy	Other malignancies could influence the interpretation of safety, efficacy, and pharmacokinetic study	No	In the EURMP, acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS) are included as an important identified risk and other SPM is included as an important potential

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
	data, in particular when assessing the incidence of second primary malignancies (SPM).		risk. These risks are adequately addressed through the risk minimisation and pharmacovigilance measures presented in Part V and Part III of theRMP, respectively.
Cardiac Function	Cardiac dysfunction not related to thalidomide therapy could influence the interpretation of the study data, in particular that regarding the safety of thalidomide.	No	Ischaemic heart disease is included as an important potential risk in the EURMP. This risk is adequately addressed through the risk minimisation and pharmacovigilance measures presented in Part V and Part III of the RMP, respectively. Section 4.2 of the SmPC states that patients should be monitored for cardiac events and dose delay, reduction or discontinuation may be necessary. Section 4.4 of the SmPC provides warnings and precautions regarding some of the potential cardiac effects of thalidomide treatment. Section 4.5 of the SmPC advises that caution should be exercised with medical products having the same pharmacodynamics effect as thalidomide due to its known potential to induce bradycardia, and Section 4.8 of the SmPC lists cardiac events that have been observed in the clinical setting.
Thrombosis	MM is associated with an increased risk of developing TEEs.[20,22] Such concomitant diseases could influence the interpretation of the study data.	No	Section 4.2 of the SmPC states that patients should be monitored for TEEs and dose delay, reduction or discontinuation may be necessary. This section also states that thromboprophylaxis should be administered for at least 5 months prior to treatment with thalidomide. Warnings and precautions regarding venous and TEEs are provided in Section 4.4 of the SmPC. Thromboembolic events are listed as an undesirable events in Section 4.8 of the SmPC.

2.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect rare adverse reactions. The short expected survival time of patients with MM means that the clinical development programme is unlikely to detect adverse reactions with a long latency or those caused by prolonged exposure. Furthermore, MM patients are predominantly elderly with a limited natural life expectancy.

2.4.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

To ensure patient safety, specific populations of patients were excluded from the clinical trials. Thus, experience in these populations is limited. Exposure of special populations is presented in Table 2.4.3-1.

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme.
Lactating women	Not included in the clinical development programme.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Not included in the clinical development programme.
Patients with renal impairment	Not included in the clinical development programme.
Patients with cardiovascular impairment	Not included in the clinical development programme.
Immunocompromised patients	Not included in the clinical development programme.
Patients with a disease severity different from inclusion criteria in clinical trials	Data from the cooperative group and company-sponsored clinical trials form the basis for the use of thalidomide as a first line treatment for patients with MM. The majority of patients recruited to the combination therapy clinical trials presented with Stage II and III MM (155 and 276 patients, respectively, corresponding to 94.7 and 209.0 patient-years), with fewer patients presenting with Stage I disease (29 patients, corresponding to 16.2 patient- years; see Section 2.3.2).
Population with relevant different ethnic origin	No formal studies have been performed in patients of different racial or ethnic origins. Although postmarketing data includes information on the use of thalidomide in different racial and ethnic populations, patients recruited to the clinical trials were predominantly White/Caucasian with only 18 and 7 patients being black or other/unknown (representing 13.5 and 4.4 patient-years, respectively) in the combination therapy clinical trials (see Section 2.3.2).
Subpopulations carrying relevant genetic polymorphisms	Genetic polymorphisms have not been studied in the thalidomide clinical trial population.

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Other	**Paediatric Population:** Not included in the clinical development programme. All patients recruited in the 3 clinical trials were > 18 years of age. **Elderly Population:** As presented in Section 2.3.2, 151 male patients and 148 female patients who were ≥ 65 years of age received thalidomide in combination therapy clinical trials, corresponding to 103.3 and 102.0 patient-years, respectively. In NDMM Study MM-020, 188 (34.4%) patients in the MPT arm (N = 547) were aged > 75 years.

2.5 Post-Authorization Experience

2.5.1 Method Used to Calculate Exposure

The methodology for estimating commercial patient exposure utilizes up to 3 data sources:[50]

1) BMS's Sales/Shipment Data – this data consists of all shipments of BMS product to all applicable countries and includes commercial and free-of-charge units for both branded and generic product (as applicable). The data are used to determine the units (eg, milligrams) of a product that was sold to a geography to estimate the number of patients who would have been exposed to that product, based on expected dosing in the geography. Shipment data are used to estimate the active patients for a period of time by dividing the total units sold by the average units per patient (note that average units per patient is derived from epidemiologic or market research).
2) Claims Data – these data consist of 2 distinct sources of electronic health care claims data in the USA: Optum Clinformatics Datamart and Symphony Claims for Hem/Onc. Claims data consisting of distinct patient IDs and prescription fill rates for each product are used to understand usage patterns.
3) Controlled Distribution Database – this data source provides detailed patient exposure including demographics, indication for use, and dosing information in the USA.

2.5.2 Exposure

Cumulatively, as of 09-Oct-2021, it is estimated that 529,631 patients have been exposed to commercial thalidomide worldwide, including 164,248 patients in the EEA and 196,612 in the US.[50]

A summary of cumulative worldwide exposure by region is provided in Table 2.5.2-1.

Table 2.5.2-1: Cumulative Thalidomide Commercial Exposure by Indication and Region through 09-Oct-2021

Indication	Total[a]	Region					
		EEA[b]	UK	USA	Canada	Australia/New Zealand	ROW[c]
MM	104,067	NA	NA	104,067	NA	NA	NA
ENL	669	NA	NA	669	NA	NA	NA
Other	73,566	NA	NA	73,566	NA	NA	NA
Unknown[d]	362,239	164,248	56,529	29,000	4572	35,324	72,566
Subtotal	540,541	164,248	56,529	207,302	4572	35,324	72,566
IIT Exposure[e]	(10,910)	0	0	(10,690)	(220)	0	0
Adjusted Total	529,631	164,248	56,529	196,612	4352	35,324	72,566

Note: Details on indication were derived from the US REMS database.

[a] Cumulative = number of unique patients exposed; it is not a sum of the individual periods. Individual periods represent exposure for the period and include newly exposed patients plus repeat patients that have been receiving treatment.

[b] EEA: Includes the 27 EU countries, Norway, Iceland, Liechtenstein.

[c] Includes countries and regions not otherwise specified in the table.

[d] Includes 29,000 patients who received thalidomide prior to the creation of S.T.E.P.S.®

[e] Subjects enrolled in IITs in the USA and Canada who are exposed to thalidomide receive product through the US REMS or Canada RevAid program respectively. Their exposure is counted as part of the non-BMS-sponsored studies.

2.5.3 Exposure within the EU/EEA Member States

Thalidomide has been launched or made available on the market at different time points in each Member State; therefore, the available data, presented in Table 2.5.3-1 and Table 2.5.3-2, do not represent the same period of time.

Table 2.5.3-1: Thalidomide Exposure by Indication and Country from the Implemented Controlled Access Programme up to 09-Oct-2021

Country	Number of Patients (%)													
	Exposure Cumulative Period													
	MM		MDS		Amyloidosis		Myelo-fibrosis		CLL		Other		Total Exposure	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Austria	858	60	16	1	9	1	18	1	2	0	531	37	1,434	100
Belgium	4,727	78	61	1	26	0	155	3	0	0	1,087	18	6,056	100
Croatia	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cyprus	412	93	1	0	1	0	8	2	1	0	18	4	441	100
Czech Republic	1	100	0	0	0	0	0	0	0	0	0	0	1	100
Estonia	318	99	0	0	0	0	0	0	0	0	3	1	321	100
France	10,388	75	104	1	44	0	21	0	0	0	3,292	24	13,849	100
Greece	2,268	92	3	0	0	0	86	3	0	0	121	5	2,478	100
Hungary	3,979	97	8	0	0	0	0	0	0	0	102	2	4,089	100
Ireland	749	81	2	0	10	1	35	4	0	0	124	13	920	100
Italy	23,648	94	36	0	181	1	194	1	0	0	997	4	25,056	100
Latvia	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lithuania	780	100	0	0	0	0	0	0	0	0	1	0	781	100
Luxembourg	76	70	0	0	0	0	1	1	0	0	32	29	109	100
Malta	75	96	0	0	0	0	0	0	0	0	3	4	78	100
Poland	100	88	1	1	1	1	8	7	0	0	4	4	114	100
Portugal	19,476	78	70	0	32	0	329	1	0	0	5,197	21	25,104	100
Romania	307	97	0	0	0	0	0	0	0	0	8	3	315	100
Slovakia	329	97	0	0	0	0	0	0	0	0	11	3	340	100
Slovenia	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Spain	4,932	69	162	2	36	1	173	2	3	0	1,791	25	7,097	100
UK	0	0	0	0	0	0	0	0	0	0	5	100	5	100
Total	73,423	83	464	1	340	0	1,028	1	6	0	13,327	15	88,588	100

Thalidomide is not commercially marketed in the following countries: Croatia, Czech Republic, Latvia.

Comments:

Austria: Current Austrian exposure to reflect DLP 09 Oct 2021 covers the period between 01 Oct 2020 and 30 Sep 2021.

Belgium: Updated to reflect DLP 09 Oct 2021. Cumulative: 30 patients with unknown indications, 44 patients with inconclusive indication (more than 1 indication for same patient) are counted as Other. 15 patients reported with indication Myelofibrosis+MM counted as Myelofibrosis, 10 patients reported with indication Amyloidosis+MM counted as amyloidosis.

Cyprus	Since 20 Dec 2019, Cyprus is no longer capturing exposure data for thalidomide. Subsequently, currently available data from previous reports shall remain as is, however, patient details or personal data will not be included from this report onwards respectively.
France	7 of the 121 MM patients received thalidomide for relapsed MM during the reporting period. 2,034 of the 10,388 MM patients received thalidomide for relapsed MM during the cumulative period. These data were extracted from thalidomide observatory (initial form).
Greece	The current and cumulative data include data up to the date of 20 Apr 2021. After this date, Greece is no longer capturing exposure data for thalidomide.
Hungary	The current Hungarian exposure to reflect DLP 09 Oct 2021 covers the period between 10 Oct 2020 and 09 Oct 2021. The cumulative period is 01 Apr 2017 to 09 Oct 2021. The previous method of calculation was based on number of individual patients; however, there has now been a change to the methodology used to collect patient exposure by using number of prescriptions.
Ireland	Edited for period 10 Oct 2020 to 09 Oct 2021. Current period off label: 4 (all indications were provided); patient type: 38 adults, 20 M, 1 FCBP, 17 WNCBP. Cumulative period off-label: 172; patient type: 497 M, 37 FCBP, 348 FNCBP, 38 unknown. Unknown age = 4 patients. Children = 1 patient (male).
Italy	Please note that for MM for first line per label (MM induction VTD) and 648 MM maintenance, data are underestimated: starting from the 01 Jan 2013 the AIFA National Oncology Registry was changed and updated information is not available. Underestimated data from the new registry are available, but data regarding patient age and risk category are not available.
Lithuania	After the RMP update, no further information is captured for Lithuania.
Luxembourg	Updated to reflect DLP 09 Oct 2021. Cumulative: 2 patients with unknown indication are counted as Other.
Malta	As of 21 Jun 2019 Malta is no longer capturing exposure data for thalidomide.
Poland	The previous method of calculation was based on sales data; however, there has now been a change to the methodology used to collect patient exposure by using RMP data. Effective for this period and onward, the methodology used will now be based on RMP data. For cumulative exposure period: indication data were not provided for 29 patients and both MM and osteomyelofibrosis were indicated for 1 patient; risk group was not provided for 50 patients, age was not provided for 27 patients.
Romania	Number of patients cover the reporting period of 10 Oct 2020 to 22 May 2021.
Slovakia	Updated to reflect DLP 09 Oct 2021. The current period is 10 Oct 2020 to 09 Oct 2021. The cumulative period is 11 Jun 2009 to 09 Oct 2021.
Slovenia	Update to reflect DLP 09 Oct 2021. Information regarding local country exposure data for thalidomide in Slovenia is not available.
Spain	Thalidomide is not launched in Spain. Exposure data updated to reflect DLP 09 Oct 2021. Data on FCBP are not available in Spain.
UK	The implemented controlled distribution system does not capture real time data linked to medicinal product dispense. Data are collected retrospectively and presented in annual reports with a defined period covered. These annual reports are provided in the EU-specific Annex of the PSUR per period covered. The cumulative data provided reflect data up to 09 Oct 2018.

Table 2.5.3-2: Thalidomide Exposure by Indication and Country based on Surrogates for Off-label Use* up to 09-Oct-2021

Country	Number of Patients (%)													
	Exposure Cumulative Period													
	MM		MDS		Amyloi-dosis		Myelo-fibrosis		CLL		Other		Total Exposure	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Denmark	0	0	0	0	0	0	0	0	0	0	2	100	2	100
Finland	0	0	0	0	0	0	1	20	0	0	4	80	5	100
Iceland	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Norway	0	0	0	0	0	0	0	0	0	0	4	100	4	100
Sweden	0	0	0	0	0	0	0	0	0	0	10	100	10	100
Total	0	0	0	0	0	0	1	5	0	0	20	95	21	100

Comments:

Denmark: From the date of launch of thalidomide on 25 Aug 2008 in Denmark until 31 Oct 2019, in total two queries have been received regarding the use in pain treatment and for pulmonary use. During 10 Oct 2019 to 31 Oct 2019 no queries about off-label use have been received. No cumulative data available from 01 Nov 2019 as this is no longer a requirement by the NCA due to the low number of queries. Off-label use will be monitored via AEs/ADRs received in off-label indications as surrogate markers.

Finland: From the date of launch of thalidomide on 19 Nov 2008 in Finland until 19 Aug 2019, in total five queries have been received regarding the use in myelofibrosis (1), dermatology (2), haemangioma (1) and in paediatrics (1). No cumulative data are available from 20 Aug 2019 as this is no longer a requirement by the NCA due to low numbers of queries. Off-label use will be monitored via AEs/ADRs received in off-label indications as surrogate markers.

Iceland: From the date of launch of thalidomide on 01 Sep 2011 in Iceland until 23 Oct 2019, no queries about off-label use have been received. No cumulative data are available from 24 Oct 2019 as this is no longer a requirement by the NCA due to low numbers of queries. Off-label use will be monitored via AEs/ADRs received in off-label indications as surrogate markers.

Norway: From the date of launch of thalidomide on 01 Sep 2008 in Norway until 09 Dec 2019, in total four queries have been received regarding the use in angiodysplasia, in children, in children using a probe to administer and granulomatous cheilitis/Melkersson-Rosenthal syndrome. During 10 Oct 2019 to 09 Dec 2019 no queries about off-label use have been received. No cumulative data are available from 10 Dec 2019 as this is no longer a requirement by the NCA due to low numbers of queries. Off-label use will be monitored via AEs/ADRs received in off-label indications as surrogate markers.

Sweden: From the date of launch of thalidomide on 10 Jun 2008 in Sweden until 09 Oct 2021, in total ten queries have been received covering the use in graft-versus-host disease (2), Morbus Osler (1), skin disorders (unspecified) (1), glioblastoma (1), ASCT eligible NDMM patients (unspecified) (1), oral cancer (1), thalassemia intermedia (1) and use in women of childbearing potential (WCBP) (2). During 10 Oct 2020 to 09 Oct 2021, 3 queries concerning the use of thalidomide were received for thalassemia intermedia (1) and use in WCBP (2), only the thalassemia intermedia case could be determined as off-label use.

Data on EU Member States as pertains to exposure in adults, females of childbearing potential and paediatric use (where such data are available) are presented in Table 2.5.3-3 and Table 2.5.3-4. Cumulatively, as of 09-Oct-2021, of the patients who received thalidomide via the controlled access programme in the EU at least 66,443 were treated for MM. It was estimated that no additional patients were treated for MM in those countries in which patient exposure was estimated

from surrogates for off-label use. Where demographic data have been documented, it is estimated that 3256 female patients of childbearing potential received thalidomide cumulatively.

Table 2.5.3-3: Thalidomide Patient Exposure by Country from the Implemented Controlled Access Programme up to 09-Oct-2021

Country	Number of Patients (%)											
	Exposure Cumulative Period											
	MM		Off-label		Adults		FCBP		Children		Total Exposure	
	N	%	N	%	N	%	N	%	N	%	N	%
Austria	858	60	576	40	0	0	0	0	0	0	1,434	100
Belgium	4,727	78	1,329	22	6,038	100	357	6	18	0	6,056	100
Croatia	0	0	0	0	0	0	0	0	0	0	0	0
Cyprus	412	93	29	7	440	100	10	2	1	0	441	100
Czech Republic	1	100	0	0	0	0	0	0	0	0	1	100
Estonia	318	99	3	1	318	99	0	0	2	1	321	100
France	10,388	75	3,461	25	13,735	99	1,136	8	114	1	13,849	100
Greece	2,268	92	210	8	2,455	99	61	2	23	1	2,478	100
Hungary	3,979	97	110	3	4,089	100	86	2	0	0	4,089	100
Ireland	749	81	171	19	915	99	37	4	1	0	920	100
Italy	23,648	94	1,408	6	NA	NA	NA	NA	NA	NA	25,056	100
Latvia	0	0	0	0	0	0	0	0	0	0	0	0
Lithuania	780	100	1	0	781	100	0	0	0	0	781	100
Luxembourg	76	70	33	30	108	99	6	6	1	1	109	100
Malta	75	96	3	4	78	100	1	1	0	0	78	100
Poland	100	88	14	12	113	99	3	3	2	2	114	100
Portugal	19,476	78	5,628	22	NA	NA	1,665	7	NA	NA	25,104	100
Romania	307	97	8	3	315	100	6	2	0	0	315	100
Slovakia	329	97	11	3	NA	NA	NA	NA	NA	NA	340	100
Slovenia	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Spain	4,932	69	2,165	31	6,925	98	NA	NA	172	2	7,097	100
UK	0	0	5	100	4	80	3	60	1	20	5	100
Total	73,423	83	15,165	17	36,314	41	3,371	4	335	0	88,588	100

Thalidomide is not commercially marketed in the following countries: Croatia, Czech Republic, Latvia.

Comments:

Austria: Current Austrian exposure to reflect DLP 09 Oct 2021 covers the period between 01 Oct 2020 and 30 Sep 2021.

Belgium: Updated to reflect DLP 09 Oct 2021 - Cumulative: indication: 1,329 off-label (including 29 others, 30 unknown, 44 inconclusive); age range: 18 children confirmed, 5,818 adults confirmed, 219 unknown (counted as adults in the table); patient type: 3,338 M, 2,318 WNCBP, 357 WCBP, 2 unknown, 41 inconclusive.

Cyprus	Since 20 Dec 2019, Cyprus is no longer capturing exposure data for thalidomide. Subsequently, currently available data from previous reports shall remain as is, however, patient details or personal data will not be included from this report onwards respectively.
France	7 of the 121 MM patients received thalidomide for relapsed MM during the reporting period. 2,034 of the 10,388 MM patients received thalidomide for relapsed MM during the cumulative period. 1 of the 37 FCBP are patients under 18 years (reporting period). 29 of the 1,129 FCBP are patients under 18 years (cumulative period). These data were extracted from thalidomide observatory (initial form).
Greece	The current and cumulative data include data up to the date of 20 Apr 2021. After this date, Greece is no longer capturing exposure data for thalidomide.
Hungary	The current Hungarian exposure to reflect DLP 09 Oct 2021 covers the period between 10 Oct 2020 and 09 Oct 2021. The cumulative period is 01 April 2017 to 09 Oct 2021. The previous method of calculation was based on number of individual patients; however, there has now been a change to the methodology used to collect patient exposure by using number of prescriptions.
Ireland	Edited for period 10 Oct 2020 to 09 Oct 2021: 4 off-label (all indications were provided); patient type: 38 adults, 20 M, 1 FCBP, 17 WNCBP. Cumulative Period: 171 off-label; patient type: 497 M, 37 FCBP, 348 FNCBP, 38 unknown. Unknown age = 4 patients. Children = 1 patient (male).
Italy	Please note that for MM for first line per label (MM induction VTD) and 648 MM maintenance, data are underestimated: starting from the 01 Jan 2013 the AIFA National Oncology Registry was changed and updated information is not available. Underestimated data from the new registry are available, but data regarding patient age and risk category are not available.
Lithuania	After the RMP update, no further information is captured for Lithuania.
Luxembourg	Updated to reflect DLP 09 Oct 2021. Cumulative: 33 off-label (including 2 unknown); age range: 1 child, 108 adults (2 unknown have been counted as adults in the table).
Malta	As of 21 June 2019, Malta is no longer capturing exposure data for thalidomide.
Poland	The previous method of calculation was based on sales data; however, there has now been a change to the methodology used to collect patient exposure by using only RMP data. Effective for this period and onward, the methodology used will now be based on RMP data. For cumulative exposure period: indication data were not provided for 29 patients and for 1 patient both MM and osteomyelofibrosis were indicated; risk group was not provided for 50 patients, age was not provided for 27 patients.
Portugal	Total exposure current reporting period: 584. Portugal current total period includes 6 prescriptions where the indication is unknown. There are 37 prescriptions that could not be adjudicated to one specific age group, as well as prescriptions with no indication for gender or disease. Cumulative period: 25,104. Portugal cumulative exposure total includes 717 prescriptions where the indication is unknown.
Romania	Updated to reflect DLP 09 Oct 2021. The current period is 10 Oct 2020 to 09 Oct 2021.
Slovakia	Updated to reflect DLP 09 Oct 2021. The current period is 10 Oct 2020 to 09 Oct 2021. The cumulative period is 11 Jun 2009 to 09 Oct 2021. Exposure data are not available for adults, FCBP, and children.
Slovenia	Updated to reflect DLP 09 Oct 2021. Information regarding local country exposure data for thalidomide in Slovenia is not available.
Spain	Thalidomide is not launched in Spain. Exposure data updated to reflect DLP 09 Oct 2021. Data on FCBP are not available in Spain.
UK	The implemented controlled distribution system does not capture real time data linked to medicinal product dispense. Data are collected retrospectively and presented in annual reports with a defined period covered. These annual reports are provided in the EU-specific Annex of the PSUR per period covered. The cumulative data provided reflect data up to 09 Oct 2018.

Table 2.5.3-4: Thalidomide Patient Exposure by Country Based on Surrogates for Off-label Use* up to 09-Oct-2021

Country	Number of Patients (%)											
	Exposure Cumulative Period											
	MM		Off-label		Adults		FCBP		Children		Total Exposure	
	N	%	N	%	N	%	N	%	N	%	N	%
Denmark	0	0	2	100	2	100	0	0	0	0	2	100
Finland	0	0	5	100	4	80	0	0	1	20	5	100
Iceland	0	0	0	0	0	0	0	0	0	0	0	0
Norway	0	0	4	100	2	50	0	0	2	50	4	100
Sweden	0	0	8	80	10	100	2	20	0	0	10	100
Total	0	0	19	90	18	86	2	9	3	14	21	100

Comments:

Denmark: From the date of launch of thalidomide on 25 Aug 2008 in Denmark until 31 Oct 2019, in total two queries have been received regarding the use in pain treatment and for pulmonary use. During 10 Oct 2019 to 31 Oct 2019 no queries about off-label use have been received. No cumulative data available from 01 Nov 2019 as this is no longer a requirement by the NCA due to the low numbers of queries. Off-label use will be monitored via AEs/ADRs received in off-label indications as surrogate markers.

Finland: From the date of launch of thalidomide on 19 Nov 2008 in Finland until 19 Aug 2019, in total five queries have been received regarding the use in myelofibrosis (1), dermatology (2), haemangioma (1) and in paediatrics (1). No cumulative data available from 20 Aug 2019 as this is no longer a requirement by the NCA due to low numbers of queries. Off-label use will be monitored via AEs/ADRs received in off-label indications as surrogate markers.

Iceland: From the date of launch of thalidomide on 01 Sep 2011 in Iceland until 23 Oct 2019, no queries about off-label use have been received. No cumulative data available from 24 Oct 2019 as this is no longer a requirement by the NCA due to the low numbers of queries. Off-label use will be monitored via AEs/ADRs received in off-label indications as surrogate markers.

Norway: From the date of launch of thalidomide on 01 Sep 2008 in Norway until 09 Dec 2019, in total four queries have been received regarding the use in angiodysplasia, in children, in children using a probe to administer and granulomatous cheilitis/Melkersson-Rosenthal syndrome. During 10 Oct 2019 to 09 Dec 2019 no queries about off-label use have been received. No cumulative data is available from 10 Dec 2019 as this is no longer a requirement by the NCA due to low numbers of queries. Off-label use will be monitored via AEs/ADRs received in off-label indications as surrogate markers.

Sweden: From the date of launch of thalidomide on 10 Jun 2008 in Sweden until 09 Oct 2021, in total ten queries have been received covering the use in graft-versus-host disease (2), Morbus Osler (1), skin disorders (unspecified) (1), glioblastoma (1), ASCT eligible NDMM patients (unspecified) (1), oral cancer (1), thalassemia intermedia (1) and use in women of childbearing potential (WCBP) (2). During 10 Oct 2020 to 09 Oct 2021, 3 queries concerning the use of thalidomide were received for thalassemia intermedia (1) and use in WCBP (2), only the thalassemia intermedia case could be determined as off-label use.

2.6 Additional EU Requirements for the Safety Specification

2.6.1 Potential for Misuse for Illegal Purposes

The hypnosedative properties of thalidomide have been studied and have shown a unique mode of action distinct from benzodiazepines and barbiturates. Based on the pharmacological properties of thalidomide, no specific risks of abuse or misuse are expected and no potential for dependence has been identified.

To date, no new safety signal has been identified relating to the misuse or abuse of thalidomide.

2.7 Identified and Potential Risks

2.7.1 Identification of Safety Concerns in the Initial RMP Submission

The summary of the safety concerns in the initial RMP submission (Version 6.0) at time of authorisation (16-Apr-2008) is presented in Table 2.7.1-1. A description of the changes to the list of safety concerns in the approved RMPs is presented in Annex 8.

Table 2.7.1-1: Safety Concerns in the Initial RMP

Important identified risks	Teratogenicity
	Peripheral Neuropathy
	Thromboembolic events (limited to venous thromboembolic events)
	Severe skin reactions
	Bradycardia/syncope
	Somnolence
	Dizziness
	Neutropenia/leukopenia
	Gastrointestinal disorders
	Thyroid dysfunction and hypothyroidism
Important potential risks	Interaction with oral contraceptives
	Off-label use
Missing information	Specific studies in hepatic impairment
	Specific studies in MM patients with renal impairment
	Paediatric patients
	Women who are breastfeeding

2.7.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Adverse reactions with minimal clinical impact on patients and not associated with any relevant risk (in relation to the life-threatening haematologic disease being treated) include somnolence and dizziness.

Adverse reactions that may have serious consequences, but occurring with a low frequency and considered to be acceptable (in relation to the life-threatening haematologic disease being treated), include severe skin reactions, gastrointestinal disorders (gastrointestinal obstruction, gastrointestinal perforation and gastrointestinal haemorrhage), thyroid dysfunction/hypothyroidism, tumour lysis syndrome, allergic conditions (hypersensitivity and angioedema/urticaria), pulmonary hypertension, interaction with oral contraceptives and convulsions.

Adverse reactions of peripheral neuropathy, TEEs, neutropenia/leukopenia, and bradycardia and syncope are already well known to HCPs and are not considered to impact the benefit-risk profile

of thalidomide in the target population. The HCPs have appropriate measures in place and the SmPC contains advice in Section 4.4 on specific clinical actions to be taken to minimise these risks.

2.7.1.2 *Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP*

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
Important identified risks	
Teratogenicity	Thalidomide is a powerful human teratogen, inducing a high frequency of severe and life-threatening birth defects. Thalidomide must never be used by women who are pregnant or by women who could become pregnant unless all the conditions of the Thalidomide BMS PPP are met. The conditions of the Thalidomide BMS PPP must be fulfilled for all male and female patients (SmPC Sections 4.3, 4.4, 4.6, 4.8, 5.2 and 5.3). See Section 2.7.3 for more details.
Severe Infections (Sepsis, Septic Shock and Viral Reactivation of Hepatitis B)	Severe infections (eg, fatal sepsis including septic shock and viral reactivation) have been observed following treatment with thalidomide in the postmarketing setting (SmPC Sections 4.4 and 4.8) and can be life-threatening or fatal depending on the severity. Pneumonia is listed as a common event in Section 4.8 of the SmPC. See Section 2.7.3 for more details.
Acute Myeloid Leukaemia and Myelodysplastic Syndromes	Acute myeloid leukaemia and MDS have been observed in clinical trials following treatment with thalidomide (SmPC Sections 4.4 and 4.8) and may result in significant morbidity and mortality. See Section 2.7.3 for more details.
Important potential risks	
Ischaemic Heart Disease (Including Myocardial Infarction)	Myocardial Infarction has been observed following treatment with thalidomide in the postmarketing setting (SmPC, Sections 4.4 and 4.8). Ischaemic heart disease can be life-threatening or fatal depending on the severity, and can impact activities of daily living. Additional cardiac events of cardiac failure and bradycardia are listed as common events in Section 4.8 of the SmPC. See Section 2.7.3 for more details.
Other Second Primary Malignancies	An increased incidence of SPM has been observed in patients with NDMM receiving lenalidomide (SmPC, Section 4.4), which is structurally related to thalidomide. SPM may result in significant morbidity and mortality, depending on the type of malignancy, and can impact the patient's activities of daily living. See Section 2.7.3 for more details.
Hepatic Disorders (Hepatocellular and Cholestatic Liver Injury)	Hepatic disorders, mainly abnormal liver test results, have been reported following treatment with thalidomide (SmPC, Sections 4.4 and 4.8) and may result in significant morbidity and mortality depending on the severity and may impact activities of daily living. See Section 2.7.3 for more details.

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
Off-label Use	Off-label use in the EU is >15% and thalidomide has been used in the 1960s for off-label use in morning sickness during pregnancy. See Section 2.7.3 for more details.
Missing Information	
None	

2.7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

There are no changes to the Safety Concerns proposed.

2.7.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

This section presents detailed characterisation of the safety concerns under their proposed classification (ie, Important Identified/Potential Risk or Missing Information). The data presented in this section are taken from the individual clinical study reports (CSRs; IFM 99-06, THAL-MM-003 and E1A00), extensive postmarketing experience and published literature (see References in Appendix 1).

Although comparators and methods of data collection and reporting varied across studies, consideration was given to the results from pooled analyses in addition to individual studies.

2.7.3.1 Presentation of Important Identified and Important Potential Risks

Table 2.7.3.1-1: Important Identified Risk: Teratogenicity

Important Identified Risk: Teratogenicity	
Potential mechanisms	The mechanism by which thalidomide causes birth defects is not completely understood, although various theories suggest that it may disturb the migration of neural crest cells during early embryogenesis, inhibit angiogenesis, and/or down-regulate adhesion receptors on early limb bud cells and on cells of the heart in embryos.[53,54]
Evidence source and strength of evidence	Thalidomide is a known powerful human teratogen, inducing a high frequency (about 30%) of severe and life threatening birth defects. A study in cynomolgus monkeys further confirmed the teratogenic effect of thalidomide, with observations such as shift of the preputium to the left in 1 foetus, and in 2 foetuses severe malformations such as oligo- and/or polydactyly, shortened, absent and/or flexed parts of the extremities, and correlating skeletal findings as known from the thalidomide syndrome in humans. Although women of childbearing potential taking thalidomide are particularly at risk, partners of men taking thalidomide are also at risk as thalidomide may be present in semen.
Characterization of risk	There were no cases of pregnancy reported in the 3 clinical trials.

Table 2.7.3.1-1: Important Identified Risk: Teratogenicity

Important Identified Risk: Teratogenicity

As of 09-Oct-2021 there have been a total of 91 reports of pregnancy reported in EU countries, non-EU countries and the US through the TRMP/PPP, ATU and Thalidomide REMS™, as well as reports from India (the MAH does not market thalidomide in India and has therefore not instituted a pregnancy prevention strategy in that country). Of these cases, a total of 21 occurred in a European country (3 in female patients, 17 in female partners, and 1 non-patient exposure), with 14 cases received from France, 2 each from the UK and Spain, and 1 each from Germany, Belgium and Sweden.

The types of exposure and outcomes of the 91 pregnancies are summarised in the table below.

	Number of Exposed Pregnancies	**Outcome**
Pregnancy of treated female patients	10	Induced abortion: n = 4 Normal live birth: n = 3 Spontaneous abortion: n = 1 Missed abortion: n = 1 Pending: n = 1
Pregnancy of female partners of treated male patients	58	Normal live birth: n = 33 Unknown: n = 17 Induced abortion: n = 3 Spontaneous abortion: n = 2 Ectopic pregnancy: n =1 Twin with one showing abnormal range of motion: n = 1 Live birth with abdominal wall defect: n = 1
Non-patient exposure (accidental exposure via skin)	23[a]	Unknown: n = 17 Normal live birth: n = 5 Spontaneous miscarriage attributed to an unspecified genetic trait: n = 1

[a] One report of death in utero (heart failure/hygromas of the spine) is not included because the female had no contact with thalidomide capsules or any body fluids of the treated patient.

Risk factors and risk groups

The 'at risk' group comprises female patients of childbearing potential or female partners of male patients treated with thalidomide.

Preventability

To avoid any risk of foetal exposure to thalidomide, the drug is contraindicated in women who are pregnant or who are at risk of becoming pregnant unless all the conditions of the PPP are met. In addition, thalidomide is contraindicated in male patients unable to follow or comply with the required contraceptive measures, due to the possibility of thalidomide presence in semen. If pregnancy does occur during treatment, the drug should be discontinued immediately.

Impact on the risk-benefit balance of the product

Thalidomide is a powerful human teratogen, inducing a high frequency (about 30%) of severe and life threatening birth defects such as: ectromelia (amelia, phocomelia, hemimelia) of the upper and/or lower extremities, microtia with abnormality of the external acoustic meatus (blind or absent), middle and internal ear lesions (less frequent), ocular lesions (anophthalmia, microphthalmia), congenital heart disease and renal abnormalities. Other less

Table 2.7.3.1-1: Important Identified Risk: Teratogenicity

Important Identified Risk: Teratogenicity	
	frequent abnormalities have also been described (SmPC, Section 4.6). Alimentary tract, urinary tract and genital malformations have also been documented.[55] A single dose of thalidomide taken during pregnancy can cause severe birth defects. The risk is extremely high between approximately 21 to 35 days after conception, a crucial time for the development of the limbs and major organ systems.[44] The risk of other potentially severe birth defects outside this critical period is unknown. Normal deliveries have been reported in thalidomide-exposed mothers; however, these appear to have been due to thalidomide exposure outside the sensitive period of gestation.[56] The impact on the patient can be potentially severe or life-threatening defects/disability, or foetal death.
Public health impact	In 30% of pregnancies exposed to thalidomide, children are born with severe defects and the rate of mortality at or shortly after birth is approximately 40%.[57] There is concern that thalidomide may eventually be used in countries that may not require stringent control of marketing, distribution and prescription.
Data Source	Studies IFM 99-06, THAL-MM-003 and E1A00; data from the TRMP/PPP, ATU and Thalidomide REMS™.
MedDRA Terms	MedDRA PTs: pregnancy, pregnancy of partner, pregnancy test positive, drug exposure during pregnancy, blood hCG positive.

Table 2.7.3.1-2: Important Identified Risk: Severe Infections (Sepsis, Septic Shock and Viral Reactivation of Hepatitis B)

Important Identified Risk: Severe Infections (Sepsis, Septic Shock and Viral Reactivation of Hepatitis B)	
Potential mechanisms	The mechanism for thalidomide-associated severe infection has not been identified. In some cases, an increased risk of infection may result from the drug's immunomodulatory effects.[58] Thalidomide has been shown to have anti-TNFα effects, which increases the risk of opportunistic infection.[59]
Evidence source and strength of evidence	Severe infections (eg, fatal sepsis including septic shock) have been observed following treatment with thalidomide in the postmarketing setting and can be life-threatening or fatal depending on the severity. Pneumonia is listed as a common event in Section 4.8 of the SmPC. Viral infections, including herpes zoster and hepatitis B virus reactivation have been observed following treatment with thalidomide in the postmarketing setting (SmPC, Section 4.8).
Characterization of risk	**Frequency with 95% CI** Across the 3 clinical trials, events of severe infections (sepsis and septic shock) were reported in 5 (1.1%; 95% CI: 0.5%-2.5%) thalidomide-treated patients. The incidence for patients unexposed to thalidomide was 1.14%, giving a RR of severe infections (sepsis and septic shock) of 0.95 (95% CI: 0.31-2.93) in thalidomide-treated patients. The incidence of severe infections (sepsis and septic shock) in the overall population (including the comparator arms) was 1.11%. The excess risk due to thalidomide was −0.05%.

Table 2.7.3.1-2: Important Identified Risk: Severe Infections (Sepsis, Septic Shock and Viral Reactivation of Hepatitis B)

Important Identified Risk: Severe Infections (Sepsis, Septic Shock and Viral Reactivation of Hepatitis B)	
	Across the 3 clinical trials, there were reports of viral reactivation of hepatitis B virus (HBV) in 2 (0.4%) thalidomide-treated patients (PTs hepatitis B and chronic hepatitis B in 1 [0.2%] patient each). No events of viral reactivation of HBV were reported in patients unexposed to thalidomide. **Seriousness/Outcomes** In Study E1A00, no serious event of severe infections (sepsis or septic shock) was reported. In Study IFM99-06, 1 thalidomide-treated patient experienced a septic shock. The outcome of this SAE was unknown. In Study Thal-MM-003, 4 (1.7%) thalidomide-treated patients experienced serious events of severe infections. Among them, 1 patient had septic shock, 1 patient had endotoxic shock, 1 patient had circulatory collapse, and 1 patient had both septic shock and vascular shock. Five patients discontinued study drug due to these events: 1 due to septic shock, 1 due to endotoxic shock, 1 due to circulatory collapse, 1 due to vascular shock, 1 due to both vascular shock and septic shock. One patient had study drug interruption due to both septic shock and vascular shock. There were no serious events of viral reactivation of HBV reported across the 3 clinical trials. **Severity and Nature of Risk** All of the events of severe infections (sepsis and septic shock) experienced by thalidomide-treated patients were Grade 3 or 4 in intensity, with the exception of 1 Grade 5 case of septic shock in Study IFM 99-06. In these 3 studies, only 2 patients in thalidomide-treated group had dose interruption. One patient in thalidomide-treated group and 1 patient in thalidomide unexposed group had dose discontinuation. There have been no events of viral reactivation of HBV of Grade 3 or 4 intensity, and no events leading to dose interruption or discontinuation across the 3 clinical trials.
Risk factors and risk groups	Numerous disease-related and chemotherapy-induced factors render the subject with cancer at increased risk for infection.[60] These include the type of cancer, depth and duration of neutropenia, and impairments in cellular function caused by cytotoxic or immunosuppressive drugs; breaches in the integument from surgical procedures, presence of indwelling plastic venous catheters, or mucositis of the gastrointestinal tract secondary to chemotherapy; and comorbid conditions such as malnutrition, deconditioning, or medical problems such as chronic obstructive lung disease or diabetes. In addition, steroid therapy induces a broad immunosuppressive effect, including impaired chemotaxis and killing by neutrophils, impaired T-cell function, and alterations in skin and mucosal barriers. Long-term or high-dose steroid therapy is a significant risk factor for invasive fungal infections in particular; such therapy also may predispose affected subjects to development of bacterial infections and *Mycobacterium tuberculosis* reactivation. Iron overload and cigarette smoking are also risk factors for infection.[61] Hepatitis B virus persists for decades in patients following recovery from acute HBV infection, during which it is controlled by the immune system. Therefore, situations that lead to immunosuppression in patients with chronic HBV infection may alter the natural history of this infection and give rise to reactivation.

Table 2.7.3.1-2: Important Identified Risk: Severe Infections (Sepsis, Septic Shock and Viral Reactivation of Hepatitis B)

Important Identified Risk: Severe Infections (Sepsis, Septic Shock and Viral Reactivation of Hepatitis B)	
	Risk factors for HBV reactivation include baseline HBV DNA > 10^5 copies/mL, baseline ALT levels, HBeAg seropositivity, corticosteroid therapy, anthracyclines, rituximab, male sex, younger age, and underlying disease of lymphoma or breast cancer.[62,63]
Preventability	Severe infections are not unexpected in this high risk patient population. No specific increased risk for severe infections is expected in patients treated with thalidomide in combination with other antimyeloma agents. No specific recommendation is warranted for patients already being monitored in routine medical practice for infectious complications due to their underlying disease and concomitant treatment. However, due to its immunomodulatory activity, the contributing role of thalidomide in an increased susceptibility to infections, including severe infections, could not be totally excluded. Section 4.4 of the EU SmPC highlights the need to monitor for severe infections, including sepsis and septic shock, and viral reactivation, including active HBV infection, throughout therapy. This section warns that HBV reactivation has been reported in patients receiving thalidomide and some cases led to acute hepatic failure and discontinuation of thalidomide, advises that HBV status should be established before initiating treatment with thalidomide and recommends that for patients who test positive for HBV infection, a physician with expertise in the treatment of hepatitis B should be consulted. Caution is advised when thalidomide is used in patients previously infected with HBV. Section 4.8 of the SmPC lists severe infections and viral infections, including herpes zoster virus and HBV reactivation, as ADRs.
Impact on the risk-benefit balance of the product	Infection may affect activities of daily living, be life-threatening or fatal depending on the severity.
Public health impact	MM and chronic lymphocytic leukaemia patients have been shown to have a 15-fold increased rate of infection compared to age-matched patients. Infection is a major cause of death in MM patients, with 18% to 33% of serious infections resulting in death. A large study using population-based data from Sweden to estimate the risk of bacterial and viral infections among 9610 MM patients compared to 37,718 matched controls demonstrated that MM patients had a 6-fold (hazard ratio = 5.9; 95% CI = 5.7-6.1) risk of developing any infection compared to matched controls.[64] Infection is frequently associated with early mortality in subjects with MM. Herpes zoster virus-specific cell-mediated immunity keeps VZV in latency and prevents its reactivation.[65] Reviews have reported that the prevalence of latent VZV in the normal population ranges from 63% to 100%.[66] A retrospective analysis reported that in general, MM patients have shown a risk of VZV infection of 1% to 4%, increasing with bortezomib treatment or transplants.[67] HBV persists for decades in patients following recovery from acute HBV infection during which it is controlled by the immune system. Therefore, situations that lead to immunosuppression in patients with chronic HBV infection may alter the natural history of this infection and give rise to reactivation. Patients should be monitored for severe infections including sepsis and septic shock and cases of viral reactivation have been reported in patients receiving thalidomide (SmPC, Section 4.4). Infections should be treated aggressively in MM patients, as these contribute significantly to morbidity and mortality.[68] These infections may necessitate treatment with

Table 2.7.3.1-2: Important Identified Risk: Severe Infections (Sepsis, Septic Shock and Viral Reactivation of Hepatitis B)

Important Identified Risk: Severe Infections (Sepsis, Septic Shock and Viral Reactivation of Hepatitis B)	
	antibiotics and/or G-CSF for neutropenic infection. The majority of patients with MDS die from bleeding or infection due to bone marrow failure.[69].
Data Source	Studies IFM 99-06, THAL-MM-003 and E1A00.
MedDRA Terms	MedDRA PTs of circulatory collapse, endotoxic shock, septic shock, and shock. These terms will be collectively referred to as severe infections (sepsis and septic shock). HBV reactivation: Study Thal-MM-003, SMQ of hepatitis B virus (MedDRA v15.1). Studies IFM 99-06 and E1A00, PTs of adenoviral hepatitis, anti-HBs antibody positive, asymptomatic viral hepatitis, congenital hepatitis B infection, Gianotti-Crosti syndrome, hepatitis B, hepatitis B antibody, hepatitis B antibody abnormal, hepatitis B antibody negative, hepatitis B antibody normal, hepatitis B antibody positive, hepatitis B antigen, hepatitis B antigen positive, hepatitis B core antigen, hepatitis B core antigen positive, hepatitis B DNA assay, hepatitis B DNA assay negative, hepatitis B DNA assay positive, hepatitis B e antigen, hepatitis B e antigen negative, hepatitis B e antigen positive, hepatitis B immunisation, hepatitis B positive, hepatitis B surface antigen, hepatitis B surface antigen negative, hepatitis B surface antigen positive, hepatitis B test negative, hepatitis B virus, hepatitis infectious, hepatitis infectious mononucleosis, hepatitis post transfusion, hepatitis viral and hepatitis viral test (MedDRA v9).

Table 2.7.3.1-3: Important Identified Risk: Acute Myeloid Leukaemia and Myelodysplastic Syndromes

Important Identified Risk: Acute Myeloid Leukaemia and Myelodysplastic Syndromes	
Potential mechanisms	No mechanism whereby thalidomide may cause SPM has been identified. While none of the following may be exclusive there may be several explanations why patients with MM might develop secondary haematopoietic and lymphatic cancers, including: • **Treatment related** Change of natural disease history as a result of improved survival in recent years As a consequence of the use of alkylating agents Prolonged immunosuppression (cytopenias) Use of G CSF, especially in combination with high dose chemotherapy Increased surveillance of cancer patients As a consequence of selective reporting • **Syndromic** Cytogenetic factors associated with MM Heredity • **Shared Etiologic Factors** HHV 8 infection in the case of Kaposi sarcoma EBV infection in the case of PTLD Exposure to environmental agents (hypothetical)

Table 2.7.3.1-3: Important Identified Risk: Acute Myeloid Leukaemia and Myelodysplastic Syndromes

Important Identified Risk: Acute Myeloid Leukaemia and Myelodysplastic Syndromes	
Evidence source and strength of evidence	In clinical trials and postmarketing data, SPM have been reported in patients treated with thalidomide as well as with drugs in the same class. A statistically significant increase of AML and MDS has been observed in 1 clinical trial in patients with previously untreated MM receiving the combination of melphalan, prednisone, and thalidomide (MPT; SmPC, Section 4.4). Based on study MM-020, in patients receiving MPT, the haematologic SPM incidence rate (0.72 per 100 patient years) was increased as compared to lenalidomide in combination with dexamethasone (0.17 per 100 patient years).
Characterization of risk	**Frequency with 95% CI** No AML/MDS was reported in Studies IFM99-06, Thal-MM-003 or E1A00. **Seriousness/Outcomes** None. **Severity and Nature of Risk** None.
Risk factors and risk groups	Travis has recently grouped second primary cancers into 3 major groups based on the predominant etiologic factors ie, treatment-related, syndromic, and those due to shared etiologic factors, while emphasising the nonexclusivity of these groups.[29] Possible explanations for the epidemiologic findings presented in the previous section will be discussed below. • **Prolonged Survival as a Result of Improved Therapies** Due to improvements in the care of patients with cancer, the number of cancer survivors has been increasing in recent years. Increased longevity increases the risk of developing a second malignancy, whether due to the late sequelae of treatment, lifestyle factors, environmental exposures, or host factors (eg, aging, genetic factors, gene-environment interactions), or a combination of these factors. Second solid tumours are a leading cause of mortality among several populations of long-term survivors. Therapy-associated solid tumours are thought to be most commonly associated with radiotherapy, with a latency period typically greater than 10 years. Radiotherapy in the context of MM is most commonly employed in the treatment of solitary plasmocytomas and for palliation of skeletal lesions.[29] As reported from the SEER Cancer Statistics Review 1975 to 2007, the 5-year RS among MM patients has increased from 26% among patients first diagnosed in 1975 to 1977 to 38% among patients first diagnosed between 1999 and 2006. Among patients aged less than 65 years at first diagnosis, 5-year RS is 50.6%; among those aged 65 years and older, survivorship is 28.1%.[70] • **Exposure to Alkylating Agents** The risk of developing MDS and/or AML following the use of alkylating agents has been recognised for several decades and the risk may increase with increasing cumulative dose. The risk of AML begins to increase at 1 to 2 years, and peaks at 5 to 10 years followed by a decrease afterwards. In many cases there is a preceding MDS, including chromosomal abnormalities. Alkylating agents linked to human leukaemia include busulfan, carmustine, chlorambucil, cyclophosphamide, dihydroxybusulfan, lomustine, mechlorethamine, melphalan, prednimustine, and semustine.[29] One of the best-characterised and most potent leukemogenic alkylating drugs is melphalan.[71]

Table 2.7.3.1-3: Important Identified Risk: Acute Myeloid Leukaemia and Myelodysplastic Syndromes

Important Identified Risk: Acute Myeloid Leukaemia and Myelodysplastic Syndromes	
	• **Cytogenetic Markers** Interestingly, chromosomal anomalies of the same types that are seen in primary AML are seen in most cases of therapy-associated MDS or AML.[72] Therapy-associated AML or MDS are well-recognised complications of therapy in MM patients. Significant transformation risk extends for many years following therapy. Cytogenetic studies have identified specific karyotypes that are regularly associated with specific cytotoxic exposures, and these karyotypes have implications for both the development of MDS/AML and for survivorship. • **Lymphoproliferative Disorders in ASCT Patients** The development of PTLD after solid organ transplantation is well recognised.[73] Most cases are due to EBV-driven tumour formation in B cells. Other important risks include the use of potent and prolonged immunosuppressive medication, the age of donor (in the case of allogenic transplantation) and recipient, number and severity of rejection episodes and cytokine gene polymorphisms.[73] In patients with MM a number of prospective, randomised trials have been conducted that compare conventional chemotherapy with high-dose therapy using ASCT. As a result of these studies, ASCT has nowadays become a standard of care in MM.[74] However, these patients are at risk of developing PTLD. Reports have demonstrated that haematopoietic stem cell transplantation (SCT) patients with PTLD generally have higher concentrations of EBV DNA in the peripheral blood than patients without PTLD.[75] • **Granulocyte Colony-stimulating Factor Therapy** Recent guidelines for cancer care support the use of G-CSF prophylaxis in specific therapeutic circumstances.[76] Despite the usefulness of G-CSF therapy, increased risks of AML or MDS associated with G-CSF use have been described. Lyman recently provided a systematic review of AML/MDS incidence among 6058 and 6746 patients randomly assigned to receive chemotherapy with and without initial G-CSF support in 25 randomised clinical trials.[77] At mean and median follow-up across studies of 60 and 53 months, respectively, AML/MDS was reported in 22 control patients and 43 G-CSF patients, for an estimated RR of 1.92 (95% CI: 1.19-3.07; p = 0.007). Median follow-up time was 54 months. The risk of AML/MDS was significantly increased in studies where G-CSF use was associated with higher total dose of chemotherapy (RR = 2.334; 95% CI: 1.237-4.403; p = 0.009). There was no significant difference in the RR for mortality. Even though these findings do not establish a unique causal role associated with the use of G-CSF the median follow-up of about 5 years may be insufficient to provide a final quantification of AML/MDS. • **Heredity** Additional insight has also been obtained in elucidating the risk of malignancies in close family members of patients affected by MM. The available data show an increased risk of more than 1 malignancy in MM patients and first degree relatives compared to the general population. The reason for this finding is still unclear but may clearly involve risk conferred by shared genetic factors.[78,79]
Preventability	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

Table 2.7.3.1-3: Important Identified Risk: Acute Myeloid Leukaemia and Myelodysplastic Syndromes

Important Identified Risk: Acute Myeloid Leukaemia and Myelodysplastic Syndromes	
	prednisone. Physicians should carefully evaluate patients before and during treatment using standard cancer screening and institute treatment as indicated (SmPC, Section 4.4).
Impact on the risk-benefit balance of the product	Acute myeloid leukaemia and MDS may result in significant morbidity and mortality. It can impact the patient's activities of daily living.
Public health impact	Dores undertook an analysis of all second primary cancers among 23,838 MM patients in the SEER-9 Cancer Registries from 1973 to 2000.[26] Non-melanoma skin cancers are not reportable to the SEER programme and therefore are not included in these data. The authors reported that among patients of all ages, the overall risk of second primary cancer was not increased (standardised incidence ratio [SIR] = 0.98; 95% CI 0.93-1.04). Despite these findings, research has identified an elevated risk of specific forms, in particular MDS, AML, NHL and Kaposi sarcoma in North American and European populations. Increased risk of second cancer was shown in the SEER analysis by Dores for patients less than 70 years of age (SIR = 1.09).[26] Within this age group, increased risks were associated with AML (SIR = 13.43), Kaposi sarcoma (SIR = 4.89), melanoma of skin (SIR = 1.67) and cancer of the urinary bladder (SIR = 1.62). Among subjects aged ≥ 70 years, significantly increased risks were observed for AML (SIR = 4.62) and for chronic myeloid leukaemia (SIR = 2.79). In this study, the risk for NHL was not significantly elevated over the entire time period, but was noted to be significantly elevated at 5 to 9 years (SIR = 2.02) and most of these may be assumed to be B-cell malignancies. Among patients of all ages in the SEER analysis, the risk of AML in MM patients was highly elevated overall (SIR = 8.32) and followed an inverted-U curve by duration of follow-up, with statistically significant risk increases noted at 1 to 4 years of follow-up (SIR = 7.21), 5 to 9 years of follow-up (SIR = 18.53) and > 10 years of follow-up (SIR = 11.52). Cannon, looking at SEER data for MM and Kaposi sarcoma during the period 1973 to 1995, found significant associations between MM and Kaposi sarcoma (SIR = 5.42), NHL (SIR = 1.51), cancer of the urinary bladder (SIR = 1.42), the colon (SIR = 1.25) and of the prostate (SIR = 1.13), including synchronous cases diagnosed at the same time as MM that were excluded from the previous study.[80] Dong summarised the risk of second primary neoplasms among 8656 myeloma patients in the Swedish Family Cancer Database 1958 to 1996.[27] Overall, 475 subsequent malignancies were observed. Again, the overall risk of a second malignancy was not increased (SIR = 0.94). However, the aggregate risk of haematolymphoproliferative disorders was significantly elevated (SIR = 2.19), driven primarily by a significantly increased risk for myeloid leukaemia (SIR = 8.19) and NHL (SIR = 1.74). The risk of developing myeloid leukaemia was greatest 1 to 9 years after the initial diagnosis (SIR = 9.50). In a large systematic evaluation of population-based data from Sweden,Mailankody found that compared to the general population, MM patients had a 1.26-fold increased risk of developing any secondary malignancy and an 11-fold increased risk of developing AML/MDS.[28] In exploratory analyses, the authors demonstrated that the risk of AML/MDS among MM patients diagnosed prior to the introduction of IMiDs (pre 2000 in Sweden; SIR = 13.51 [95%CI 8.83-19.80]) was not significantly different to patients diagnosed after IMiDs introduction (follow-up until 2006, ie, when thalidomide was the only IMiD in use; SIR = 8.35 [95%CI 4.17-14.94]). However, as the actual usage of IMiD therapy in Sweden

Table 2.7.3.1-3: Important Identified Risk: Acute Myeloid Leukaemia and Myelodysplastic Syndromes

Important Identified Risk: Acute Myeloid Leukaemia and Myelodysplastic Syndromes	
	during the study period was relatively low and the follow-up time restricted, these analyses should be interpreted with caution. One large clinical case series by Hasskarl described the occurrence of metachronous malignancy among 589 myeloma patients identified during 1997 to 2008 at a large university centre in Germany. Of interest, 41/589 patients (7%) had a malignancy other than MM diagnosed either prior to or at the same time as MM.[30] These prior or synchronous neoplasms were composed of colorectal (7), gynaecologic (7), skin including melanoma (6), renal-urothelial (6), prostate (4), and others. There were 7 lymphomas diagnosed, of which 6 were mature B-cell neoplasms which occurred prior to or synchronously. Fewer patients experienced second cancer after an MM diagnosis (18/589; 3%). Among the latter, haematologic malignancies, specifically AML/MDS, were the most common, being identified at the same time in 1 patient and after the MM diagnosis in 5 patients. As survival after a diagnosis of cancer improves, identification and quantification of the late effects of cancer and its therapy have become critical. Generally, new cancer is considered to be one of the most serious events experienced by cancer survivors. The number of patients with multiple primary cancers is growing rapidly, with independent malignancies now comprising about 16% of incident cancers reported to the National Cancer Institute's SEER programme in 2003. Moreover, second tumours may be a cause of mortality among several populations of long-term survivors.[29] In patients with Hodgkin's disease, the 5-year OS rate following a second malignancy was around 38%, but only about 5% following a diagnosis of AML.[81] It should be noted, however, that the risk of dying from MM is considerably higher than the risk of developing a second cancer.[82]
Data Source	Studies IFM 99-06, THAL-MM-003, E1A00 and MM-020. A cumulative safety review of SPM was completed and submitted in Mar 2011. The BMS Safety Database was searched for reports of SPM with thalidomide from first in human exposure until 28-Feb-2011. All sources of cases, regardless of causality and medical confirmation, were included. A further update to the STR was submitted in Jun 2012, following an observation of a numerical imbalance of cases of AML and MDS in Study MM-020. In Sep 2012, supplementary information of clinical and safety data from Studies MM-020 and MM-015 was requested by CHMP which was submitted in Nov 2012. A post-approval measure response document was submitted on 06 Sep 2013 to provide updated SPM analyses for Study MM-020 when the median follow-up time for survival reached 36 months. On 21-Nov-2013, the CHMP outcome was adopted endorsing the MAH's conclusions and agreeing with the results of the longer follow-up; incidence rates of haematologic and solid tumour SPMs in the MPT arm of Study MM-020 were consistent with those observed for the earlier data cut-off date of Jul 2012 submitted in Nov 2012.
MedDRA Terms	• **AML** HLT of Leukaemias acute myeloid, PTs of acute promyelocytic leukaemia differentiation syndrome, acute leukaemia and acute leukaemia in remission. • **MDS** HLT of myelodysplastic syndromes.

Table 2.7.3.1-4: Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction)

Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction)	
Potential mechanisms	In theory, MI events may occur on the same aetiological basis as the thrombotic events that have been reported with thalidomide. The incidence of TEEs appears higher in cancer patients treated with thalidomide in combination with steroids and other chemotherapeutic agents. Although the precise mechanism is unknown, several theories have been proposed, including the contribution of the underlying disease state and a procoagulant effect of thalidomide on chemotherapy damaged endothelium.
Evidence source and strength of evidence	In clinical trials, events of MI were reported more frequently in patients treated with thalidomide. MI has been reported in patients receiving thalidomide in the postmarketing setting, particularly in those with known risk factors (SmPC, Sections 4.4 and 4.8); Ischaemic heart disease, including MI, can be life-threatening or fatal depending on the severity, and can impact activities of daily living. Other cardiac events, such as Cardiac failure and bradycardia are listed as common events in Section 4.8 of the SmPC.
Characterization of risk	**Frequency with 95% CI** Across the 3 clinical trials, events of MI were reported in 26 (5.65%; 95% CI: 3.7% 8.2%) thalidomide treated patients. The incidence for patients unexposed to thalidomide was 2.9%, giving a RR of MI of 1.99 (95% CI: 1.07 3.70) in thalidomide treated patients. The incidence of MI in the overall population (including the comparator arms) was 4.2%. The excess risk due to thalidomide was 49.6%. **Seriousness/Outcomes** A total of 6 reports of serious MI were recorded in thalidomide-treated patients in the clinical trials (1 and 5 reports, respectively, in Studies IFM 99-06 and THAL-MM-003). The outcomes of the 5 SAEs from Study THAL-MM-003 are summarised below. The outcome of the SAE in Study IFM 99-06 is unavailable.

Outcome	**Number of Cases**
Death	1
Recovered/resolved	1
Recovered with sequelae	3
Total	5

Severity and Nature of Risk

A maximum of 3 thalidomide-treated patient reported Grade 3 or 4 MI AEs in Study IFM 99-06 (WHO toxicology code). In Studies THAL-MM-003 and E1A00, a maximum of 9 and 2 thalidomide-treated patients, respectively, reported Grade 3 or 4 MI AEs (NCI CTC). In addition, 3 thalidomide-treated patients reported Grade 5 MI AEs in Study E1A00. Due to different methods of data presentation, it is not known whether different types of events may have been reported for the same patient. Therefore, the actual number of patients who experienced Grade 3, 4 or 5 MI may be less than the maximum numbers reported above. For similar reasons, it is difficult to determine precise numbers, but approximately 10 and

Table 2.7.3.1-4: Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction)

Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction)	
	1 reports of Grade 1 or 2 MI were also recorded in thalidomide-treated patients in Studies THAL-MM-003 and E1A00, respectively. In the IFM 99-06 trial, no severe MI events led to drug discontinuation or dose reduction/interruption in thalidomide-treated patients. In the THAL-MM-003 trial, severe MI events led to drug discontinuation in 1 thalidomide-treated patient and to dose interruption or reduction in 2 thalidomide-treated patients. In Study E1A00, the specific events leading to discontinuation, interruption, or reduction of study drug were not collected.
Risk factors and risk groups	In addition to advanced age, there are many established risk factors for MI, such as hereditary factors, male gender, smoking, diabetes mellitus, endstage renal disease and excessive dietary fat. Common comorbidities among MI patients aged 65 years and older include congestive heart failure, hypertension, and diabetes.[83] Additional known risk factors include hypercholesterolemia and sedentary lifestyle.[84] Furthermore MM is characterised by a proliferation of malignant plasma cells, and a subsequent overabundance of monoclonal paraprotein. The overproduction of these paraproteins may lead to hyperviscosity, amyloidosis, and renal failure. It has been suggested that hyperviscosity occasionally can lead to increased viscosity of the blood, resulting in complications such as stroke, myocardial ischaemia, or infarction.[85]
Preventability	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 (eg, smoking, hypertension, and hyperlipidaemia) (SmPC, Section 4.4).
Impact on the risk-benefit balance of the product	Ischaemic heart disease can be life-threatening or fatal depending on the severity, and can impact activities of daily living.
Public health impact	Information on the incidence/prevalence of MI in the EU is limited. Among 5148 participants in the Rotterdam prospective cohort study of persons at least age 55 with no evidence of prevalent infarction, 141 recognised MIs occurred and the incidence rate of this event was 5.0 per 1000 patient-years.[86] The incidence was higher in men (8.4) than in women (3.1). The incidence of unrecognised MI was 3.8 per 1000 patient -years, with only small differences between men (4.2) and women (3.6). Rates generally increased with age for both recognised and unrecognised MI. In a population-based cohort of 3729 people older than 64 years identified in 3 geographical areas of Spain and free of previous MI, adjusted incidence rates of MI were higher in men (957 per 100,000 patient -years) than in women (546 per 100,000).[87] Thus, men showed a significantly ($p < 0.001$) higher cumulative incidence of MI at 10 years (7.2%) than women (3.8%). While cumulative incidence increased with age ($p < 0.05$), gender-differences tended to narrow. Using linked Hospital Episode Statistics and mortality information, the Oxford Record Linkage studied English individuals of any age, who were admitted to hospital for AMI or who died suddenly from AMI in 2010.[88] They identified 82,252 AMI events. Age-standardised incidence of first AMI per 100,000 population was 130 (95% CI: 129-131) in men and 55.9 (95% CI: 55.3–56.6) in women. Incidence rates demonstrated a steep age

Table 2.7.3.1-4: Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction)

Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction)	
	gradient for both men and women, with about three-quarters of all AMIs occurring in individuals aged ≥ 65 years. About 1 in 6 AMIs are reinfarctions in both men and women, and this proportion increases with older age. Disease of the heart and circulatory system (cardiovascular disease) is the main cause of death in the EU, accounting for 1.9 million deaths each year. Forty percent of all deaths in the EU (43% of deaths in women and 36% of deaths in men) are from cardiovascular disease – slightly less than for Europe as a whole. Over a third of deaths from cardiovascular disease in the EU are from CHD. CHD by itself is the single most common cause of death in Europe and death rates from CHD are generally higher in Central and Eastern Europe than in Northern, Southern and Western Europe. CHD is also the single most common cause of death in the EU, accounting for over 681,000 deaths in the EU each year: 15% of deaths among men, and 13% of deaths among women.[89] Myocardial infarction is one of the leading causes of morbidity and mortality in developed countries. Many of the risk factors associated with MI can be modified eg, through a change in lifestyle.
Data Source	Studies IFM 99-06, THAL-MM-003 and E1A00.
MedDRA Terms	Myocardial infarction MedDRA SMQ Broad and other ischaemic heart disease MedDRA SMQ Broad will be collectively referred to as MI.

Table 2.7.3.1-5: Important Potential Risk: Other Second Primary Malignancies

Important Potential Risk: Other Second Primary Malignancies	
Potential mechanisms	No mechanism whereby thalidomide may cause other SPM has been identified. While none of the following may be exclusive there may be several explanations why patients with MM might develop secondary haematopoietic and lymphatic cancers, including: • **Treatment-related** Change of natural disease history as a result of improved survival in recent years As a consequence of the use of alkylating agents Prolonged immunosuppression (cytopenias) Use of G-CSF, especially in combination with high-dose chemotherapy Increased surveillance of cancer patients As a consequence of selective reporting • **Syndromic** Cytogenetic factors associated with MM Heredity • **Shared Etiologic Factors** HHV-8 infection in the case of Kaposi sarcoma EBV infection in the case of PTLD Exposure to environmental agents (hypothetical)

Table 2.7.3.1-5: Important Potential Risk: Other Second Primary Malignancies

Important Potential Risk: Other Second Primary Malignancies	
Evidence source and strength of evidence	In clinical trials, other SPM have been recorded in some patients receiving thalidomide.
Characterization of risk	**Frequency with 95% CI** In Study IFM 99-06, events of other SPM were reported in 3 (2.4%; 95% CI: 0.50%-6.85%) thalidomide-treated patients. The incidence for patients in the MP group (hereafter referred to as "patients unexposed to thalidomide" in this table) was 2.1%. The incidence of other SPM in the overall population (including the 2 comparator arms) was 1.6%. Adverse events of other SPM were reported by 5 (2.1%; 95% CI: 0.70%-4.92%) thalidomide-treated patients in Study THAL-MM-003. The incidence for patients unexposed to thalidomide was 1.3%. The incidence of other SPM in the overall population (including the comparator arm) was 1.7%. In Study E1A00, there were no reports of other SPM. **Seriousness/Outcomes** In Study THAL-MM-003, a total of 2 serious other SPM were recorded in 1 thalidomide-treated patient. Both these SAEs (1 SAE of carcinoma in situ and 1 SAE of colon adenoma) had outcomes recorded as recovered/resolved. In Study IFM 99-06, a total of 2 reports of serious other SPM were recorded in thalidomide-treated patients. Of these 2 SAEs, 1 (an SAE of renal cell carcinoma stage unspecified) had an outcome of death, and for the other SAE (acute lymphocytic leukaemia) the outcome was not recorded. **Severity and Nature of Risk** One (0.8%) thalidomide-treated patient reported Grade 3 or 4 other SPM in Study IFM 99-06 (WHO toxicology code). In Study THAL-MM-003, no thalidomide-treated patients reported Grade 3 or 4 other SPM (NCI CTC). In Study IFM 99-06, no other SPM led to drug discontinuation or dose reduction/interruption. In Study THAL-MM-003, other SPM led to dose interruption in 1 (0.4%) thalidomide-treated patient and to drug discontinuation in no thalidomide-treated patients.
Risk factors and risk groups	Travis has recently grouped second primary cancers into 3 major groups based on the predominant etiologic factors ie, treatment-related, syndromic, and those due to shared etiologic factors, while emphasising the nonexclusivity of these groups.[29] In the following, possible explanations for the epidemiologic findings presented in the previous section will be discussed. • **Prolonged Survival as a Result of Improved Therapies** Due to improvements in the care of patients with cancer, the number of cancer survivors has been increasing in recent years. Increased longevity increases the risk of developing a second malignancy, whether due to the late sequelae of treatment, lifestyle factors, environmental exposures, or host factors (eg, aging, genetic factors, gene-environment interactions), or a combination of these factors. Second solid tumours are a leading cause of mortality among several populations of long-term survivors. Therapy-associated solid tumours are thought to be most commonly associated with radiotherapy, with a latency period typically greater than 10 years. Radiotherapy in the context of MM is most commonly employed in the treatment of solitary plasmocytomas and for palliation of skeletal lesions.[29] As reported from the SEER Cancer Statistics Review 1975 to 2007, the 5-year RS among MM patients has increased from 26% among patients first diagnosed in 1975 to 1977 to

Table 2.7.3.1-5: Important Potential Risk: Other Second Primary Malignancies

Important Potential Risk: Other Second Primary Malignancies

38% among patients first diagnosed between 1999 and 2006. Among patients aged less than 65 years at first diagnosis, 5-year RS is 50.6%; among those aged 65 years and older, survivorship is 28.1%.[70]

- **Exposure to Alkylating Agents**

The risk of developing MDS and/or AML following the use of alkylating agents has been recognised for several decades and the risk may increase with increasing cumulative dose. The risk of AML begins to increase at 1 to 2 years, and peaks at 5 to 10 years followed by a decrease afterwards. In many cases there is a preceding MDS, including chromosomal abnormalities. Alkylating agents linked to human leukaemia include busulfan, carmustine, chlorambucil, cyclophosphamide, dihydroxybusulfan, lomustine, mechlorethamine, melphalan, prednimustine, and semustine.[29] One of the best-characterised and most potent leukemogenic alkylating drugs is melphalan.[71]

- **Cytogenetic Markers**

Interestingly, chromosomal anomalies of the same types that are seen in primary AML are seen in most cases of therapy-associated MDS or AML.[72]

Therapy-associated AML or MDS are well-recognised complications of therapy in MM patients. Significant transformation risk extends for many years following therapy. Cytogenetic studies have identified specific karyotypes that are regularly associated with specific cytotoxic exposures, and these karyotypes have implications for both the development of MDS/AML and for survivorship.

- **Lymphoproliferative Disorders in ASCT Patients**

The development of PTLD after solid organ transplantation is well recognised.[73] Most cases are due to EBV-driven tumour formation in B cells. Other important risks include the use of potent and prolonged immunosuppressive medication, the age of donor (in the case of allogenic transplantation) and recipient, number and severity of rejection episodes and cytokine gene polymorphisms.[73] In patients with MM a number of prospective, randomised trials have been conducted that compare conventional chemotherapy with high-dose therapy using ASCT. As a result of these studies, ASCT has nowadays become a standard of care in MM.[74] However, these patients are at risk of developing PTLD. Reports have demonstrated that haematopoietic SCT patients with PTLD generally have higher concentrations of EBV DNA in the peripheral blood than patients without PTLD.[75]

- **Granulocyte Colony-stimulating Factor Therapy**

Recent guidelines for cancer care support the use of G-CSF prophylaxis in specific therapeutic circumstances.[76] Despite the usefulness of G-CSF therapy, increased risks of AML or MDS associated with G-CSF use have been described. Lyman recently provided a systematic review of AML/MDS incidence among 6058 and 6746 patients randomly assigned to receive chemotherapy with and without initial G-CSF support in 25 randomised clinical trials.[77] At mean and median follow-up across studies of 60 and 53 months, respectively, AML/MDS was reported in 22 control patients and 43 G-CSF patients, for an estimated RR of 1.92 (95% CI: 1.19-3.07; p = 0.007). Median follow-up time was 54 months. The risk of AML/MDS was significantly increased in studies where G-CSF use was associated with higher total dose of chemotherapy (RR = 2.334; 95% CI: 1.237-4.403; p = 0.009). There was no significant difference in the RR for mortality. Even though these findings do not establish a unique causal role associated with the use of G-CSF the median

Table 2.7.3.1-5: Important Potential Risk: Other Second Primary Malignancies

Important Potential Risk: Other Second Primary Malignancies	
	follow-up of about 5 years may be insufficient to provide a final quantification of AML/MDS. • **Heredity** Additional insight has also been obtained in elucidating the risk of malignancies in close family members of patients affected by MM. The available data show an increased risk of more than 1 malignancy in MM patients and first degree relatives compared to the general population. The reason for this finding is still unclear but may clearly involve risk conferred by shared genetic factors.[78,79]
Preventability	Other SPM, such as AML and MDS have been reported in patients receiving thalidomide. Physicians should carefully evaluate patients before and during treatment using standard cancer screening and institute treatment as indicated (SmPC, Section 4.4).
Impact on the risk-benefit balance of the product	Other SPM may result in significant morbidity and mortality depending on the type of malignancy. It can impact the patient's activities of daily living.
Public health impact	Dores undertook an analysis of all second primary cancers among 23,838 MM patients in the SEER-9 Cancer Registries from 1973 to 2000.[26] Non-melanoma skin cancers are not reportable to the SEER programme and therefore are not included in these data. The authors reported that among patients of all ages, the overall risk of second primary cancer was not increased (SIR = 0.98; 95% CI 0.93-1.04). Despite these findings, research has identified an elevated risk of specific forms, in particular MDS, AML, NHL and Kaposi sarcoma in North American and European populations. Increased risk of second cancer was shown in the SEER analysis by Dores for patients less than 70 years of age (SIR = 1.09). Within this age group, increased risks were associated with AML (SIR = 13.43), Kaposi sarcoma (SIR = 4.89), melanoma of skin (SIR = 1.67) and cancer of the urinary bladder (SIR = 1.62).[26] Among subjects aged ≥ 70 years, significantly increased risks were observed for AML (SIR = 4.62) and for chronic myeloid leukaemia (SIR = 2.79). In this study, the risk for NHL was not significantly elevated over the entire time period, but was noted to be significantly elevated at 5 to 9 years (SIR = 2.02) and most of these may be assumed to be B-cell malignancies. Among patients of all ages in the SEER analysis, the risk of AML in MM patients was highly elevated overall (SIR = 8.32) and followed an inverted-U curve by duration of follow-up, with statistically significant risk increases noted at 1 to 4 years of follow-up (SIR = 7.21), 5 to 9 years of follow-up (SIR = 18.53) and > 10 years of follow-up (SIR = 11.52). Cannon, looking at SEER data for MM and Kaposi sarcoma during the period 1973 to 1995, found significant associations between MM and Kaposi sarcoma (SIR = 5.42), NHL (SIR = 1.51), cancer of the urinary bladder (SIR = 1.42), the colon (SIR = 1.25) and of the prostate (SIR = 1.13), including synchronous cases diagnosed at the same time as MM that were excluded from the previous study.[80] Dong summarised the risk of second primary neoplasms among 8656 myeloma patients in the Swedish Family Cancer Database 1958 to 1996.[27] Overall, 475 subsequent malignancies were observed. Again, the overall risk of a second malignancy was not increased (SIR = 0.94). However, the aggregate risk of haematolymphoproliferative disorders was significantly elevated (SIR = 2.19), driven primarily by a significantly increased risk for myeloid leukaemia (SIR = 8.19) and NHL (SIR = 1.74). The risk of developing myeloid leukaemia was greatest 1 to 9 years after the initial diagnosis (SIR = 9.50).

Table 2.7.3.1-5: Important Potential Risk: Other Second Primary Malignancies

Important Potential Risk: Other Second Primary Malignancies	
	In a large systematic evaluation of population-based data from Sweden, Mailankody found that compared to the general population, MM patients had a 1.26-fold increased risk of developing any secondary malignancy and an 11-fold increased risk of developing AML/MDS.[28] In exploratory analyses, the authors demonstrated that the risk of AML/MDS among MM patients diagnosed prior to the introduction of IMiDs (pre 2000 in Sweden; SIR = 13.51 [95%CI 8.83-19.80]) was not significantly different to patients diagnosed after IMiDs introduction (follow-up until 2006, ie, when thalidomide was the only IMiD in use; SIR = 8.35 [95%CI 4.17-14.94]). However, as the actual usage of IMiD therapy in Sweden during the study period was relatively low and the follow-up time restricted, these analyses should be interpreted with caution. One large clinical case series by Hasskarl described the occurrence of metachronous malignancy among 589 myeloma patients identified during 1997 to 2008 at a large university centre in Germany.[30] Of interest, 41/589 patients (7%) had a malignancy other than MM diagnosed either prior to or at the same time as MM. These prior or synchronous neoplasms were composed of colorectal (7), gynaecologic (7), skin including melanoma (6), renal-urothelial (6), prostate (4), and others. There were 7 lymphomas diagnosed, of which 6 were mature B-cell neoplasms which occurred prior to or synchronously. Fewer patients experienced second cancer after an MM diagnosis (18/589; 3%). Among the latter, haematologic malignancies, specifically AML/MDS, were the most common, being identified at the same time in 1 patient and after the MM diagnosis in 5 patients. As survival after a diagnosis of cancer improves, identification and quantification of the late effects of cancer and its therapy have become critical. Generally, new cancer is considered to be one of the most serious events experienced by cancer survivors. The number of patients with multiple primary cancers is growing rapidly, with independent malignancies now comprising about 16% of incident cancers reported to the National Cancer Institute's SEER programme in 2003. Moreover, second tumours may be a cause of mortality among several populations of long-term survivors.[29] In patients with Hodgkin's disease, the 5-year OS rate following a second malignancy was around 38%, but only about 5% following a diagnosis of AML.[81] It should be noted, however, that the risk of dying from MM is considerably higher than the risk of developing a second cancer.[82]
Data Source	Studies IFM 99-06, THAL-MM-003, E1A00 and MM-020. A cumulative safety review of SPM was completed and submitted in Mar 2011. The BMS Safety Database was searched for reports of SPM with thalidomide from first in human exposure until 28-Feb-2011. All sources of cases, regardless of causality and medical confirmation, were included. A further update to the STR was submitted in Jun 2012, following an observation of a numerical imbalance of cases of AML and MDS in Study MM-020. In Sep 2012, supplementary information of clinical and safety data from Studies MM-020 and MM-015 was requested by CHMP which was submitted in Nov 2012. A post-approval measure response document was submitted on 06 Sep 2013 to provide updated SPM analyses for Study MM-020 when the median follow-up time for survival reached 36 months. On 21 Nov 2013, the CHMP outcome was adopted endorsing the MAH's conclusions and agreeing with the results of the longer follow-up; incidence rates of haematologic and solid tumour SPM in the MPT arm of Study MM-020 were consistent with those observed for the earlier data cut-off date of Jul 2012 submitted in Nov 2012.
MedDRA Terms	Other SPM were separated into 3 categories for analysis: other haematologic malignancies, solid tumours and non-melanoma skin cancers. All events reported in the neoplasms system organ class (SOC) MedDRA v13.1 for postmarketing data were examined to identify cases of other haematologic malignancies, solid tumours, and non-melanoma skin cancers. For

Table 2.7.3.1-5: Important Potential Risk: Other Second Primary Malignancies

Important Potential Risk: Other Second Primary Malignancies	
	this RMP, the same approach was utilised for clinical trial data using MedDRA v9.0 for Study IFM 99-06 and MedDRA v5.1 for Study THAL-MM-003. The MedDRA HLGTs/HLTs used to identify events in the different categories are as follows: • **Other Haematologic Malignancies** HLGT of haematopoietic neoplasms (excluding leukaemias and lymphomas), HLT of leukaemias chronic myeloid, leukaemias chronic (not elsewhere classified) NEC, leukaemias chronic T-cell, leukaemias lymphocytic NEC, leukaemias NEC, HLGT lymphomas non-Hodgkin's T-cell, and HLGT of plasma cell neoplasms; HLGT of lymphomas non-Hodgkin's B-cell, HLGT of lymphomas Hodgkin's disease, HLGT of lymphomas non-Hodgkin's unspecified histology, HLT of leukaemias acute lymphocytic, HLT of leukaemias chronic lymphocytic, and HLT of lymphomas unclassifiable malignant, and PT of lymphocytic lymphoma. • **Solid Tumours** HLGTs of breast neoplasms malignant and unspecified (including nipple), endocrine neoplasms malignant and unspecified, gastrointestinal neoplasms malignant and unspecified, hepatobiliary neoplasms malignant and unspecified, mesotheliomas, miscellaneous and site unspecified neoplasms malignant and unspecified, nervous system neoplasms malignant and unspecified NEC, ocular neoplasms, renal and urinary tract neoplasms malignant and unspecified, reproductive and genitourinary neoplasms gender unspecified NEC, reproductive neoplasms female malignant and unspecified, reproductive neoplasms male malignant and unspecified, respiratory and mediastinal neoplasms malignant and unspecified, skeletal neoplasms malignant and unspecified, skin melanomas (excluding ocular), soft tissue neoplasms malignant and unspecified (excluding sarcomas), soft tissue sarcomas. • **Non-melanoma Skin Cancers** Skin neoplasms malignant and unspecified (excluding melanoma).

Table 2.7.3.1-6: Important Potential Risk: Hepatic Disorders (Hepatocellular and Cholestatic Liver Injury)

Important Potential Risk: Hepatic Disorders (Hepatocellular and Cholestatic Liver Injury)	
Potential mechanisms	Although the exact mechanism of DILI remains largely unknown, it appears to involve 2 pathways: direct hepatotoxicity and adverse immune reactions. Mostly DILI is initiated by the bioactivation of drugs to chemically reactive metabolites, which have the ability to interact with cellular macromolecules such as proteins, lipids, and nucleic acids, leading to protein dysfunction, lipid peroxidation, DNA damage, and oxidative stress. Parenchymal cell injury induces activation of innate and/or adaptive immune cells, which, in turn, produce proinflammatory and tissue hepatotoxic mediators, and/or mount immune reactions against drug-associated antigens.[90]
Evidence source and strength of evidence	In clinical trials, hepatic disorders were common events which were predominantly Grade 1 or 2 in severity. Hepatic disorders, mainly abnormal liver test results, have been reported following treatment with thalidomide in the postmarketing setting (SmPC, Sections 4.4 and 4.8) and may result in significant morbidity and mortality depending on the severity and may impact activities of daily living.

Table 2.7.3.1-6: Important Potential Risk: Hepatic Disorders (Hepatocellular and Cholestatic Liver Injury)

Important Potential Risk: Hepatic Disorders (Hepatocellular and Cholestatic Liver Injury)	
Characterization of risk	**Frequency with 95% CI** Data from Study Thal-MM-003 showed a slightly greater incidence of hepatic disorders in the placebo/dexamethasone arm compared with the thalidomide/dexamethasone arm (12.5% versus 8.9%). In Study IFM 99-06, the incidence of hepatic disorders was slightly greater in the melphalan/prednisone/thalidomide arm compared to the melphalan/prednisone arm (5.6% versus 3.0%), and the melphalan arm was (4.1%). In Study ECOG E1A00, the incidence of hepatic disorders was slightly greater in the thalidomide/dexamethasone arm than in the dexamethasone arm (68.6% versus 60.8%). The majority of the hepatic disorders were in the liver-related investigations, signs, and symptoms SMQ. **Seriousness/Outcomes** There were 291 reports of SAEs of hepatic disorders in MM patients. Of these, 188 were serious nonfatal events, with outcomes of resolved/resolving/resolved with sequelae in 69, not recovered in 18 and not provided in 101 (note: these data were taken from the STR and include other sources in addition to clinical trials). **Severity and Nature of Risk** Most liver function test abnormalities in Studies THAL-MM-003, IFM 99-06 and ECOG E1A00 were Grades 1 and 2 in intensity.
Risk factors and risk groups	Cancer chemotherapy may cause hepatic injury since drug effects may be cytotoxic for both normal and tumour cells. Recent reviews summarise current knowledge regarding hepatotoxicity associated with chemotherapeutic agents employed in the treatment of MM.[91,92] Despite its being metabolised by the liver, adverse reactions associated with cyclophosphamide have only rarely been reported. Melphalan produces transient abnormalities in liver function tests at the high doses used in autologous BMT. Doxorubicin is extensively metabolised in the liver and an increased incidence of hepatotoxicity has been reported. Bortezomib is metabolised by the liver and hyperbilirubinemia and portal vein thrombosis have been reported. Hepatic disorders with thalidomide have been described in literature (see Safety Topic Review: Review of Hepatic Disorders in Patients Treated with Thalidomide, dated 05 Dec 2011). Hepatic adverse effects have also been associated with molecular-targeted cancer treatments. Severe hepatitis has been described with the use of imatinib. Gemtuzumab and imatinib have been reported to induce autoimmune hepatitis.[93] While MM predominantly affects bone marrow and bones, myelomatous infiltration of extraosseus tissues may occur in the reticuloendothelial system, including liver, spleen, and lymph nodes. Summarising cases of MM presenting at the Mayo Clinic between 1960 to 1971 and between 1985 to 1998, Kyle and colleagues noted that a palpable liver was present in 21% and 4% of patients at the time of initial diagnosis, respectively.[94,95] Among 2584 patients treated at the Myeloma Institute for Research and Therapy from Aug 1997 to Nov 2003, 24 patients with gastrointestinal system involvement documented by tissue biopsy were identified.[37] The organ mostly commonly involved was the liver (11 patients; 0.43%). These authors noted that gastrointestinal involvement at the time of initial diagnosis is much rarer than gastrointestinal involvement later in the course of the disease and that it often develops in patients with relapsing disease after SCT. Median survival after diagnosis of gastrointestinal involvement was 7 months (range, 1 to 54 months).

Table 2.7.3.1-6: Important Potential Risk: Hepatic Disorders (Hepatocellular and Cholestatic Liver Injury)

Important Potential Risk: Hepatic Disorders (Hepatocellular and Cholestatic Liver Injury)	
	Sixty-four necropsies of patients with MM were reviewed for liver diseases.[96] Only 6 (9%) had a normal liver on histological examination; plasma cell infiltrates in the liver was noted in 56% of the patients and amyloidosis was reported in 6% to15% of patients with MM. Abnormalities of liver function tests were frequently noted and there was a relatively high incidence of jaundice.
Preventability	It is recommended that patients with severe hepatic impairment should be carefully monitored for AEs (Sections 4.2 and 4.4 of the SmPC). Patients should be monitored for liver function, particularly in case of pre-existing liver disorder or concomitant use of medication that is likely to induce liver dysfunction (Section 4.4 of the SmPC). Section 4.8 of the SmPC has also been updated with regard to the risk of hepatic disorders.
Impact on the risk-benefit balance of the product	Hepatic disorders may result in significant morbidity and mortality depending on the severity. They may impact activities of daily living.
Public health impact	DILI is infrequent but potentially an SAE. The idiosyncratic nature and poor prognosis of DILI make this type of reaction a major safety issue during drug development, as well as the most common cause for the withdrawal of drugs from the pharmaceutical market. According to the US Acute Liver Failure Study Group, DILI accounts for more than 50% of acute liver failure, including hepatotoxicity caused by overdose of acetaminophen and idiosyncratic liver injury triggered by other drugs (13%). The US FDA has removed several drugs from the market because of the significant patient morbidity and mortality associated with DILI, including bromfenac, ebrotidine, and troglitazone. Drug-induced liver injury can affect both parenchymal and non-parenchymal cells of the liver, leading to a wide variety of pathological conditions, including acute and chronic hepatocellular hepatitis, fibrosis/cirrhosis, cholestasis, steatosis, as well as sinusoidal and hepatic artery/vein damage. The predominant forms of DILI include acute hepatitis, cholestasis, and a mixed pattern. Acute hepatitis is defined as a marked increase in aminotransferases coinciding with hepatocellular necrosis. Cholestasis is characterised by jaundice with a concurrent elevation in alkaline phosphatase, conjugated bilirubin, and glutamyl transpeptidase. Mixed-pattern DILI includes clinical manifestations of both hepatocellular and cholestatic injury. The occurrence of DILI ranges from 1 in 10,000 to 1 in 100,000.[90]
Data Source	Studies IFM 99-06, THAL-MM-003 and E1A00.
MedDRA Terms	The MedDRA v14.0 SMQ of drug related hepatic disorders—comprehensive search which included sub-SMQs of cholestasis and jaundice of hepatic origin; drug related hepatic disorders—severe events only [sub-SMQs of hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions, hepatitis non infectious, liver neoplasms benign (including cysts and polyps), liver neoplasms malignant and unspecified (sub-SMQs of liver malignant tumours and liver tumours of unspecified malignancy)]; liver related investigations, signs and symptoms; and liver related coagulation and bleeding disturbances; all are collectively referred to as hepatic disorders.

Table 2.7.3.1-7: Important Potential Risk: Off-label Use

Important Potential Risk: Off-label Use
The approved indication for thalidomide in the EEA is MM. However, worldwide the approved indications vary per territory and include use outside of the EEA target population like the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum. It is also used off-label in non-haematological malignancies (eg, renal cell carcinoma, prostate cancer). Given its anti-inflammatory properties, thalidomide is also used in a variety of nonmalignant inflammatory conditions where no other treatment is available or where the disease is refractory to standard treatments (eg, systemic and discoid lupus erythematosus, Behçet's disease and prurigo nodularis). No different safety profile is expected in these off-label populations, but the risk of the safety concern of teratogenicity may be higher in these populations due to the potential younger age of the population treated resulting in a higher rate of women of childbearing potential exposed and treatment initiation by potentially not educated healthcare professionals due to a different target audience. Therefore, the additional pharmacovigilance activity of monitoring off-label use as agreed with the NCAs is instituted in the EEA. Exposure data are provided in Section 2.5.

2.7.3.2 Presentation of the Missing Information

Not applicable.

2.8 Summary of the Safety Concerns

Important identified and potential risks, together with missing information, are summarised in Table 2.8-1.

Table 2.8-1: Summary of Safety Concerns

Important identified risks	Teratogenicity
	Severe infections (sepsis, septic shock and viral reactivation of hepatitis B)
	AML and MDS
Important potential risks	Ischaemic heart disease (including myocardial infarction)
	Other SPM
	Hepatic disorders (hepatocellular and cholestatic liver injury)
	Off-label use
Missing information	None

3 PART III: PHARMACOVIGILANCE PLAN

3.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance activities in BMS as described in the BMS Pharmacovigilance System Master File and Drug Safety's Standard Operating Procedures are in accordance with the "GVP" Guidelines in the EU.

In addition to expedited reporting, BMS vigilantly undertakes follow-up on all ADRs, including serious ADRs that are provided to health authorities to ensure that all details of the case are captured for optimal clinical evaluation. This includes efforts to obtain all relevant information and to establish the final outcome of the ADRs.

Emerging potential safety signals can be detected by periodic and if appropriate, cumulative evaluation of the ADRs. The results are compiled in the PSUR with summaries and conclusions submitted to the health authorities. PSURs are submitted in accordance with "Guidelines on Good Pharmacovigilance Practices in the EU" and in accordance to the EURD list.

A status report of pregnancies in patients exposed to thalidomide or female partners of male patients exposed to thalidomide is provided in each PSUR. Each PSUR includes a comprehensive analysis of case reports including the reason for the occurrence of pregnancy.

For events of special interest, materials and tools have been developed to ensure that consistent and good quality follow-up information is obtained.See Annex 4 for forms, as applicable, summarized in Table 3.1-1.

Table 3.1-1: Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection

Specific adverse reaction follow-up questionnaires	
Event-specific questionnaires are available for the risks of Teratogenicity, Severe infections (sepsis, septic shock and viral reactivation of hepatitis B), AML and MDS, Ischaemic heart disease (including myocardial infarction), Other SPM and Hepatic disorders (including abnormal liver test results, hepatocellular and cholestatic liver injury).	For events of special interest, materials and tools have been developed to ensure that consistent and good quality follow up information can be obtained. These forms are presented in Annex 4.
Other forms of routine pharmacovigilance activities	
Other forms of routine pharmacovigilance activities for expedited reporting and follow-up of pregnancy	The PPP aims to minimise the risks of teratogenicity by ensuring HCPs and patients are fully informed of and understand the risks of teratogenicity prior to starting their thalidomide treatment. Thalidomide is an immunomodulatory agent with expected teratogenic effects in humans. The core PPP for thalidomide reflects advice, guidance and direction obtained from the Member States during the implementation process for lenalidomide and thalidomide. Where possible and with the agreement of the NCA, BMS harmonised the thalidomide PPP with the already implemented lenalidomide PPP in each Member State. In order to ensure there is a consistent approach with the ability to capture all information globally, the same principles on obtaining follow-up data on pregnancies are implemented in all territories where thalidomide is

Table 3.1-1: Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection

marketed whilst taking into account the legal and healthcare differences in those territories worldwide.

The objectives of the system are:

- To obtain information on all reported pregnancies of females exposed to thalidomide.
- To obtain information on all reported pregnancies of female partners of male patients exposed to thalidomide.
- To determine the root cause of all pregnancies and hence failures of the PPP.

In the EU, BMS uses the following method to enhance the capture of reports of pregnancy over and above reliance upon spontaneous reporting:

- The Educational HCP brochure makes reference to the requirement to report all suspected pregnancies to the local BMS office and where applicable to the NCA. The Patient Brochure also advises the patient to immediately seek medical advice if there is any risk or suspicion of possible risk of pregnancy. Similar advice is also provided with reference to female partners of male patients.

Database of Pregnancy Reports

All reports of pregnancies received by BMS are entered into BMS's Global Safety Database. This includes all Consumer reports in addition to HCP reports. Any abnormal pregnancy test results (eg, β hCG elevated and positive urine pregnancy test) are immediately processed. European Union Health Authorities are notified of these reports.

Follow-up

All reports of pregnancies are followed up. Follow-up is via the physician/obstetrician/ neonatologist/paediatrician as appropriate. In each country office, any report of pregnancy is followed up by the Drug Safety staff. All reports of pregnancy are also immediately notified to the QPPV and QPPV deputies.

All reports of abnormal pregnancy test results are followed up with the prescriber and follow-up information is sent to Health Authorities as required.

Frequency/Duration of Followup

Upon receipt of a notification of pregnancy, the follow-up questionnaire is sent to the reporter. Upon receipt of this information byBMS, dates for further follow-up actions are tracked.

The HCP/Obstetrician is to send a Follow-Up and Outcome Form to be completed at the outcome of the pregnancy.

An Infant follow-up form is available for use in the event that a birth defect is detected as an outcome.

Corresponding standard forms are available on request.

Table 3.1-1: Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection

	Root Cause of Failure of Pregnancy Prevention Programme The Pregnancy Background Form includes questions to determine why the PPP was unsuccessful for the case in question. **Regulatory Reporting of Pregnancies** All initial pregnancy reports and follow-up information is reported on an expedited basis within 15 days. Should any suspected teratogenic effect be reported following treatment with thalidomide, this is expedited immediately. Physicians are encouraged or required as per local legislation to report pregnancies to BMS and when applicable to the NCA..

3.2 Additional Pharmacovigilance Activities

A summary of ongoing and completed pharmacovigilance study protocols is provided in Annex 2.

3.2.1 Monitoring of Pregnancy Prevention Programme Implementation

Additional monitoring of implementation of the Thalidomide BMS PPP is carried out on a country specific basis in accordance with local legal framework and with the agreement of the relevant NCA (Table 3.2.1-1). Demographic data in PSURs are also being examined by country, if applicable.

In addition, reassessment of the Thalidomide BMS PPP and corrective actions will be proposed as needed. The MAH will immediately inform the relevant authorities of Members States, and the EMA, about all suspected alerts and any suspected failure in the system which may have a serious impact on public health, including the MAH's proposed actions.

Table 3.2.1-1: Monitoring of Pregnancy Prevention Programme Implementation

Study Short Name and Title	Rationale and Study Objectives	Study Design	Study Population	Milestones
Monitoring of PPP implementation.	Minimisation of the risk of teratogenicity and to provide education on the risk and the necessary steps to prevent foetal exposure.	Additional monitoring of implementation of BMS PPP on a country specific basis in accordance with local legal framework and with agreement of the relevant NCA.	Patients in the EU receiving thalidomide.	Ongoing. In line with the PSUR.

3.2.2 Additional Studies

As agreed in the EU with NCAs, some drug utilisation studies are ongoing to analyse the use and effectiveness of the risk minimisation tools, and capture at least the demographics and indication

of patients treated with Thalidomide BMS in order to monitor the off-label use of Thalidomide BMS.

3.2.3 Second Primary Malignancies Monitoring in Ongoing Studies

BMS will perform long term follow up in ongoing clinical trials to monitor SPM for BMS sponsored studies and IITs.

For Study MM-020, SPM was to be documented retrospectively and for 5 years following randomisation of the last patient. Of note, as of the DLP (09-Oct-2021) of the last PSUR, no BMS-sponsored studies were ongoing. No thalidomide BMS-sponsored clinical trial is ongoing, planned, or anticipated to be conducted in the future.

For IITs, all studies involving administration of thalidomide should include long-term follow-up to allow for collection of data with regard to SPM, preferably throughout the lifetime of the participants.

Monitoring of SPM in clinical trials is described in Table 3.2.3-1.

Table 3.2.3-1: Solicited Reporting and Long-term Follow-up of SPM

Study Short Name and Title	Rationale and Study Objectives	Study Design	Study Population	Milestones
SPM monitoring	Long-term safety evaluation and monitoring in the context of clinical trials. Monitor incidence of SPM in the clinical trial setting. Long-term follow-up of SPM in the clinical trial setting.	Solicited reporting and long-term follow-up of SPM in all BMS-sponsored clinical trials. Long-term follow-up in all BMS-sponsored clinical trials and IITs.	Patients receiving thalidomide in clinical trials.	In line with PSUR updates and CSRs

3.3 Summary Table of Additional Pharmacovigilance Activities

A summary of ongoing and planned additional pharmacovigilance activities is presented in Table 3.3-1.

Table 3.3-1: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Additional monitoring of implementation of Thalidomide BMS PPP on a country specific basis in accordance with local legal framework and with the agreement of the relevant NCA. Ongoing	Monitor implementation of BMS PPP on a country specific basis	Teratogenicity	In line with the PSUR	In line with PSUR updates
Patient materials comprehension validation. Ongoing	Monitor implementation of BMS PPP	Teratogenicity	Results provided to each NCA prior to launch	Results provided to each NCA prior to launch
Implementation of NCA agreed mechanism for monitoring off-label use. Ongoing	Monitor off-label use	Off-label use	In line with the PSUR	In line with PSUR updates
Drug utilisation studies as agreed with the NCA. Ongoing	Understand demographics of target population and number of women of child bearing potential	Teratogenicity, off-label use	In line with the PSUR	In line with PSUR updates

Table 3.3-1: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Long-term follow-up and solicited reporting of SPM in clinical trials. Ongoing	Long-term safety evaluation and monitoring of SPM in the context of clinical trials	AML/MDS, other SPM	In line with the PSUR and CSRs	In line with PSUR; updates and CSRs

4 PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no efficacy studies which are specific obligations and/or conditions of the marketing authorisation.

5 PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Important risks that are addressed by the Thalidomide BMS RMP include acknowledged concerns from product use together with potential safety signals observed during clinical trials and postmarketing experience.

The major goals of the proposed RMP for thalidomide are to prevent any foetal exposure through the Thalidomide BMS PPP, reduce risk to patients of the known elements of the safety profile of Thalidomide BMS, and to detect any changes in the benefit/risk profile such as an emerging safety signal and to evaluate risk minimisation activities.

Teratogenicity remains the most significant risk noted to date with thalidomide. While this risk is mitigated significantly by the demographics of the MM population, the Thalidomide BMS PPP is designed to further reduce the risk of foetal exposure.

The MAH is implementing a multistep approach to risk minimisation during the pre- and postlaunch periods in the EU. These activities include:

- Education, risk communication and minimisation strategies
- Risk detection and assessment by Drug Safety
- Evaluation of the Risk Management activities, including continued Risk Assessment.

Prior to launch in any Member State the exact details of the implementation of the risk minimisation activities will be agreed with each NCA and the local implementation plans.

5.1 Routine Risk Minimisation Measures

Summaries of the risk minimisation measures for the Important Identified and Potential Risks are provided in Table 5.1-1.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Teratogenicity	**Routine Risk Communication** **SmPC** Section 4.4 Special warnings and precautions for use Section 4.6 Fertility, pregnancy and lactation. Section 4.8 Undesirable effects. These sections highlight the potential teratogenic effects of thalidomide. **PL** The PL warns of the potential teratogenic effects of thalidomide and the need to avoid pregnancy.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
	Routine Risk Minimisation Activities Recommending Specific Clinical Measures to Address the Risk Thalidomide is contraindicated in pregnant women and in women of childbearing potential, unless all the conditions of the PPP are met (SmPC Section 4.3). Stringent controls are required to ensure exposure of an unborn child to thalidomide does not occur (SmPC Section 4.4). These include: • Criteria for women of non-childbearing potential • Counselling • Contraception • Pregnancy testing • Precautions for men • Additional precautions • Reference to educational materials. Section 4.6 of the SmPC provides further warnings, contraception information and advice in the case of pregnancy. Information on lactation is also provided. **Other Routine Risk Minimisation Measures Beyond the Product Information:** Thalidomide is subject to limited supply (maximum of 4 weeks for women of childbearing potential and 12 weeks for men or women of non-childbearing potential) and restricted medical prescription.
Severe Infections (Sepsis, Septic Shock and Viral Reactivation of Hepatitis B)	**Routine Risk Communication** **SmPC** Section 4.8 Undesirable effects. Listed as ADRs. **PL** The PL details the risks associated with thalidomide use, their symptoms, and any actions to be taken by the patient. This document warns that thalidomide may cause severe infections and viral reactivation. **Routine Risk Minimisation Activities Recommending Specific Clinical Measures to Address the Risk** Section 4.4 of the SmPC states that patients should be monitored for severe infections including sepsis and septic shock and that patients previously infected with hepatitis B virus should be closely monitored for signs and symptoms of viral reactivation, including active HBV infection, throughout therapy. This section also advises that HBV status should be established before initiating treatment with thalidomide and advises caution when thalidomide is used in patients previously infected with HBV. **Other Routine Risk Minimisation Measures Beyond the Product Information:** Thalidomide is subject to restricted medical prescription.
Acute Myeloid Leukaemia and Myelodysplastic Syndromes	**Routine Risk Communication** **SmPC** Section 4.8 Undesirable effects. Listed as ADRs. **PL**

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
	The PL details the risks associated with thalidomide use, their symptoms, and any actions to be taken by the patient. The PL warns of the possibility of patients developing additional types of haematological malignancies. **Routine Risk Minimisation Activities Recommending Specific Clinical Measures to Address the Risk** Section 4.4 of the SmPC states that 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. **Other Routine Risk Minimisation Measures Beyond the Product Information:** Thalidomide is subject to restricted medical prescription.
Important Potential Risks	
Ischaemic Heart Disease (Including Myocardial Infarction)	**Routine Risk Communication** **SmPC** Section 4.8 Undesirable effects Myocardial infarction as an ADR. **PL.** The PL details the risks associated with thalidomide use, their symptoms, and any actions to be taken by the patient. The PL states that patients have an increased risk of developing blood clots in the veins and arteries during treatment with thalidomide. **Routine Risk Minimisation Activities Recommending Specific Clinical Measures to Address the Risk** Section 4.2 of the SmPC gives advice regarding thromboprophylaxis, especially for those with additional thrombotic risk factors. Section 4.4 of the SmPC states that 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 (eg, smoking, hypertension, and hyperlipidaemia). **Other Routine Risk Minimisation Measures Beyond the Product Information:** Thalidomide is subject to restricted medical prescription.
Other Second Primary Malignancies	**Routine Risk Communication** **SmPC** Section 4.4 Special warnings and precautions for use Warning that other SPM such as AML and MDS have been observed after thalidomide treatment. **PL** The PL details the risks associated with thalidomide use, their symptoms, and any actions to be taken by the patient. The PL mentions the possibility of MM patients developing additional types of cancer, and a possible link to thalidomide. **Routine Risk Minimisation Activities Recommending Specific Clinical Measures to Address the Risk** Section 4.4 of the SmPC states that physicians should carefully evaluate patients before and during treatment using standard cancer screening and institute treatment as indicated.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
	Other Routine Risk Minimisation Measures Beyond the Product Information: Thalidomide is subject to restricted medical prescription.
Hepatic Disorders (Hepatocellular and Cholestatic Liver Injury)	**Routine Risk Communication** **SmPC** Section 4.8 Undesirable effects Listed as ADRs. **PL** The PL details the risks associated with thalidomide use, their symptoms, and any actions to be taken by the patient. Hepatic disorder is reflected in this leaflet. **Routine Risk Minimisation Activities Recommending Specific Clinical Measures to Address the Risk** Section 4.4 of the SmPC highlights the need to monitor patients for liver function. **Other Routine Risk Minimisation Measures Beyond the Product Information:** Thalidomide is subject to restricted medical prescription.
Off-label Use	**Routine Risk Communication** The SmPC details the risks associated with thalidomide use and actions to be taken in the event of specific AEs. Advice regarding possible side effects of thalidomide is provided in the PL. **Routine Risk Minimisation Activities Recommending Specific Clinical Measures to Address the Risk** None proposed. **Other Routine Risk Minimisation Measures Beyond the Product Information:** Thalidomide is subject to restricted medical prescription.

5.2 Additional Risk Minimisation Measures

Additional risk minimisation measures are provided in Table 5.2-1. Details of proposed additional risk minimisation activities are provided in Annex 6.

Table 5.2-1: Additional Risk Minimisation Measures

Pregnancy Prevention Programme	**Objectives:** The BMS PPP is designed to minimise the risk of teratogenicity by: • Ensuring that exposure of an unborn child to thalidomide does not occur; • Ensuring early alert to the physician of any pregnancies; • Educating patients and HCPs on the safe use of thalidomide; • Pregnancy testing and contraception requirements; • Managing and monitoring the distribution of thalidomide; • Compliance monitoring and assessment.

Table 5.2-1: Additional Risk Minimisation Measures

	Rationale for the additional risk minimisation activity: The Thalidomide BMS PPP is designed to minimise the risk of teratogenicity and provide education on the risk and the necessary steps to prevent foetal exposure. **Target audience and planned distribution path:** The target audience is HCPs who will prescribe thalidomide and patients. The key elements of the Thalidomide BMS PPP • HCP and patient education; • Classify patient risk category prior to treatment initiation; • Prescribing controls; • Dispensing controls; • Assessment. • Therapy management: Criteria for determining women of childbearing potential, effective contraceptive measures for women of childbearing potential, regular pregnancy testing for women of childbearing potential. **Plans to evaluate the effectiveness of the interventions and criteria for success:** Monitoring of implementation of BMS PPP on a country basis in agreement with relevant NCA. Expedited reporting (E+R) as per EU guidance, GVP PSUR as per EU guidance, GVP (E+R) [E = Evaluation; R = Reporting] Methods of assessment Reports of pregnancy exposure to be summarised at the time of the PSUR; Overall and by country; Root causes for pregnancy exposure; Compliance with specific elements of PPP according to country specific agreements with NCAs; Outcome of pregnancy; Modifications and corrective action will be taken accordingly. Criteria for Success Primary indicator: pregnancy exposures Proposed review period The Thalidomide BMS PPP will be analysed on an ongoing basis and will include • Description and status of the implementation in each Member State • Monitoring methodology and timelines for available data • Results of monitoring programmes when available The maximum interval of consecutive PPP compliance studies will be agreed between BMS and individual NCAs.
Additional HCP and Patient Educational Materials	**Objectives:** To ensure that the risks involved in prescribing, dispensing and taking thalidomide are clearly defined • To provide advice on reducing the drug safety concerns of thalidomide • To provide continuous education on the Thalidomide BMS PPP, and clearly describe its objectives, components, and requirements. Educational materials discuss the risks of: • Teratogenicity

Table 5.2-1: Additional Risk Minimisation Measures

	• Off-label use (HCPs only) • Ischaemic heart disease (including myocardial infarction) **Rationale for the additional risk minimisation activity:** To enable HCPs to understand the risks associated with use of thalidomide. **Target audience and planned distribution path:** Additional HCP Educational Materials are available to every prescriber, pharmacy and patient who intends to prescribe, dispense, or receive Thalidomide BMS The following non-promotional educational materials will effectively describe the Thalidomide BMS PPP with materials for both HCPs and patients: • Educational HCP brochure • Educational brochures for patients • Patient card • Risk awareness forms • Information on where to find latest SmPC Patient card The educational materials are translated and reviewed by the local Competent Authority prior to use in each Member State. Materials may be customised for each Member State based upon their Thalidomide BMS PPP implementation requirements, and possible off-label monitoring and programme assessment methods. Patient materials are provided to the national patients' organisations for review or if such an organisation does not exist or cannot be involved, by a relevant patients group, naïve to thalidomide history, to ensure that they are clearly understood. Results of the user testing will be provided to the NCA and final materials validated at a national level. An 'Educational healthcare professional's kit' has been produced, that contains the educational materials previously described, including the patient focused materials. Prior to launch in each Member State the 'Educational healthcare professional's kit' is provided to HCPs as agreed with each NCA, taking into account local medical practice and organisation. Additional copies of the educational materials are available to HCPs upon request. **Plans to evaluate the effectiveness of the interventions and criteria for success:** Methods of assessment are dependent upon the Member State implementation and may include: • AE reports to be reviewed on an ongoing basis. AEs to be analysed in the PSUR if there is a change in nature or frequency observed or significant clinical findings emerge • Monitoring the distribution of the risk minimisation tools • Risk minimisation tools sent and tracked via registered delivery • Monitoring of the utilisation and implementation of the risk awareness forms, patient card or equivalent tools • Prescriber, pharmacy and patient surveys • Compliance with specific elements of PPP according to country specific agreements with NCA. • Modifications and corrective action will be taken accordingly. Criteria for Success Primary Indicator: frequency and severity of AEs and compliance with the PPP.
Direct HCP Communication Prior to	**Objectives:** Provision of information to HCPs for the risks of: • Teratogenicity

Table 5.2-1: Additional Risk Minimisation Measures

Launch ('Dear HCP' Letter)	• Severe infections (sepsis, septic shock and viral reactivation of hepatitis B; distributed in all countries where thalidomide was marketed from Jun 2016 onwards) • Acute myeloid leukaemia and MDS (distributed in all countries where thalidomide was marketed from Apr 2013 onwards) • Off-label use • Other SPM (distributed in all countries where thalidomide was marketed from Apr 2013 onwards) **Rationale for the additional risk minimisation activity:** HCPs to understand the risks specified above and the appropriate management of these risks. **Target audience and planned distribution path:** Prior to launch in each Member State, a 'Dear Healthcare Professional' letter is sent to all relevant prescribers and pharmacies, as agreed with each NCA. **Plans to evaluate the effectiveness of the interventions and criteria for success:** Methods of assessment are dependent upon the Member State implementation and may include: • AE reports to be reviewed on an ongoing basis. AEs to be analysed in the PSUR if there is a change in nature or frequency observed or significant clinical findings emerge • Monitoring the distribution of the risk minimisation tools • Risk minimisation tools sent and tracked via registered delivery • Monitoring of the utilisation and implementation of the risk awareness forms, patient card or equivalent tools • Prescriber, pharmacy and patient surveys • Compliance with specific elements of PPP according to country specific agreements with NCA. • Modifications and corrective action will be taken accordingly. Criteria for Success Primary Indicator: frequency and severity of AEs and compliance with the PPP.

5.3 Summary of Risk Minimisation Measures

A summary of risk minimisation measures and pharmacovigilance activities by safety concern is provided in Table 5.3-1.

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Teratogenicity	**Routine Risk Minimisation Activities:** **SmPC** Section 4.3 states that thalidomide is contraindicated in pregnant women and in FCBP unless all the conditions of the BMS PPP are met. Section 4.4 provides warnings and precautions for use Section 4.6 Fertility, pregnancy and lactation. Section 4.8 where teratogenicity is listed as an ADR. **PL** This document warns of the potential teratogenic effects of thalidomide and the need to avoid pregnancy.	**Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:** • Expedited reporting of all pregnancies as a serious event • Event-specific questionnaires for collection of detailed initial and follow-up information for pregnancies for standardization (see Annex 4) • Follow-up of all pregnancies until outcome and until final diagnosis for cases of congenital malformation • Examination of demographic data in PSURs.
	Additional Risk Minimisation Activities: BMS PPP • Educational programme – Direct HCP communication prior to launch – Educational material for HCPs and patients ♦ Educational HCP brochure ♦ Risk awareness forms ♦ Patient card or equivalent tools ♦ Educational patient brochure ♦ Information on where to find latest SmPC • Therapy management: Criteria for determining women of childbearing potential, effective contraceptive measures for women of childbearing potential, regular pregnancy testing for women of childbearing potential. • Advice provided by SmPC, outlined in direct HCP communication and detailed in Educational materials.	**Additional Pharmacovigilance Activities** • Additional monitoring of implementation of Thalidomide BMS PPP on a country-specific basis in accordance with local legal framework and with the agreement of the relevant NCA: To monitor the implementation of the BMS PPP on a country-specific basis. • Patient materials comprehension validation: To monitor the implementation of the BMS PPP. • Drug utilisation studies as agreed with the NCA: To understand the demographics of the target population and number of women of child bearing potential.
Severe Infections (Sepsis, Septic Shock and Viral	**Routine Risk Minimisation Activities:** **SmPC**	**Routine pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:**

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Reactivation of Hepatitis B)	Section 4.4 where advice is given regarding the monitoring for severe infections Section 4.8 where severe infections are listed as ADRs. **PL** Advice to patients in PL, including a statement that the doctor is advised to check if the patient has ever had hepatitis B infection prior to starting thalidomide treatment. **Additional Risk Minimisation Activities:** Direct HCP communication distributed in all countries where thalidomide was marketed from Jun 2016 onwards inform HCPs of the risk of viral reactivation.	Event-specific questionnaires for collection of information for events of severe infections (see Annex 4) **Additional pharmacovigilance activities:** None.
AML and MDS	**Routine Risk Minimisation Activities:** **SmPC** Section 4.4 which warns of the risk of AML and MDS with regard to benefit of thalidomide treatment and that patients should be carefully evaluated before and during treatment. Section 4.8 where AML/MDS are listed as ADRs. **PL** Advice to patients in PL regarding the possibility of developing AML and MDS. **Additional Risk Minimisation Activities:** Direct HCP communication distributed in all countries where thalidomide was marketed from Apr 2013 onwards.	**Routine pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:** Event-specific questionnaires for collection of information for events of AML and MDS (see Annex 4) **Additional pharmacovigilance activities:** • Long-term follow-up and solicited reporting for AML and MDS in clinical trials.
Important Potential Risks		
Ischaemic Heart Disease (Including MI)	**Routine Risk Minimisation Activities:** **SmPC** Section 4.2 which provides advice regarding prophylaxis for ischaemic heart disease Section 4.4 which warns of the risk factors for myocardial infarction Section 4.8 which lists myocardial infarction as an ADR. **PL** Advice to patients in PL regarding the risk of ischaemic heart disease.	**Routine pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:** Event-specific questionnaires for collection of information for events of MI (see Annex 4) **Additional pharmacovigilance activities:** None.

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
	Additional Risk Minimisation Activities: Educational material for HCPs and patients.	
Other SPM	**Routine Risk Minimisation Activities:** **SmPC** Section 4.4 where a warning is provided that other SPMs such as AML and MDS have been observed after thalidomide treatment **PL** Advice to patients in PL regarding the risk of SPM. **Additional Risk Minimisation Activities:** Direct HCP communication distributed in all countries where thalidomide was marketed from Apr 2013 onwards.	**Routine pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:** Event-specific questionnaires for collection of information for events of SPM (see Annex 4) **Additional pharmacovigilance activities:** • Long-term follow-up and solicited reporting for other SPM in clinical trials. •
Hepatic Disorders (Hepatocellular and Cholestatic Liver Injury)	**Routine Risk Minimisation Activities:** **SmPC** Section 4.4 where clinicians are advised to monitor patients for liver function. Section 4.8 where hepatic disorders are listed as ADRs. **PL** Advice to patients in PL regarding the risk of hepatic disorders. **Additional Risk Minimisation Activities:** None	**Routine pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:** Event-specific questionnaires for collection of information for events of hepatobiliary disorders (see Annex 4) **Additional pharmacovigilance activities:** None.
Off-label Use	**Routine Risk Minimisation Activities:** • The SmPC details the risks associated with thalidomide use and actions to be taken in the event of specific AEs. • Advice to patients in PL. **Additional Risk Minimisation Activities:** • Direct HCP communication prior to launch. • Educational material for HCPs. • Agree with each Member State prior to the launch of the product the most appropriate strategies to monitor the off-label use within national territories.	**Routine pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:** None **Additional pharmacovigilance activities:** Mechanisms for monitoring off-label use will be implemented as agreed with the NCA. This may include drug utilisation studies.

6 SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for THALIDOMIDE BMS (THALIDOMIDE)

This is a summary of the risk management plan (RMP) for Thalidomide BMS. The RMP details important risks of Thalidomide BMS and how these risks can be minimised.

Thalidomide BMS's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare providers (HCPs) and patients on how Thalidomide BMS should be used.

This summary of the RMP for Thalidomide BMS should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Thalidomide BMS's RMP.

I. The medicine and what it is used for

Thalidomide BMS in combination with melphalan and prednisone is indicated for the first line treatment of patients with untreated multiple myeloma (MM), aged ≥ 65 years or ineligible for high dose chemotherapy (see SmPC for the full indication). It contains thalidomide as the active substance and it is given by oral route of administration.

Further information about the evaluation of Thalidomide BMS's benefits can be found in Thalidomide BMS's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000823/WC500037052.pdf.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Thalidomide BMS, together with measures to minimise such risks and the proposed studies for learning more about Thalidomide BMS's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Thalidomide BMS, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Thalidomide BMS are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Thalidomide BMS. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected. Important identified and potential risks, together with missing information, are summarised in the table below.

List of important risks and missing information

Important identified risks	Teratogenicity
	Severe infections (sepsis, septic shock and viral reactivation of hepatitis B)
	AML and MDS
Important potential risks	Ischaemic heart disease (including myocardial infarction)
	Other SPM
	Hepatic disorders (hepatocellular and cholestatic liver injury)
	Off-label use
Missing information	None

II.B Summary of important risks

Important identified risks

Teratogenicity	
Evidence for linking the risk to the medicine	Thalidomide is a known powerful human teratogen, inducing a high frequency (about 30%) of severe and life-threatening birth defects. A study in cynomolgus monkeys further confirmed the teratogenic effect of thalidomide, with observations such as shift of the preputium to the left in 1 foetus, and in 2 foetuses severe malformations such as oligo- and/or polydactyly, shortened, absent and/or flexed parts of the extremities, and correlating skeletal findings as known from the thalidomide syndrome in humans. Although women of childbearing potential taking thalidomide are particularly at risk, partners of men taking thalidomide are also at risk as thalidomide may be present in semen.
Risk factors and risk groups	The 'at risk' group comprises female patients of childbearing potential or female partners of male patients treated with thalidomide.
Risk minimisation measures	**Routine Risk Minimisation Activities:** **Summary of Product Characteristics (SmPC)** Section 4.3 states that thalidomide is contraindicated in pregnant women and in females of childbearing potential (FCBP) unless all the conditions of the BMS Pregnancy Prevention Plan (PPP) are met. Section 4.4 provides warnings and precautions for use Section 4.6 Fertility, pregnancy and lactation. Section 4.8 where teratogenicity is listed as an adverse drug reaction (ADR). **PL** The Package Leaflet (PL) warns of the potential teratogenic effects of thalidomide and the need to avoid pregnancy. **Additional Risk Minimisation Activities:** BMS PPP • Educational programme – Direct HCP communication prior to launch – Educational materials for HCPs and patients ♦ Educational HCP brochure ♦ Risk awareness forms ♦ Patient card or equivalent tools ♦ Educational patient brochure ♦ Information on where to find latest SmPC • Therapy management: Criteria for determining women of childbearing potential, effective contraceptive measures for women of childbearing potential, regular pregnancy testing for women of childbearing potential. • Advice provided by SmPC, outlined in direct HCP communication and detailed in Educational materials.

Important identified risks

Additional pharmacovigilance activities	Additional monitoring of implementation of Thalidomide BMS PPP on a country-specific basis in accordance with the local legal framework and with the agreement of the relevant National Competent Authority (NCA): To monitor the implementation of the BMS PPP on a country-specific basis. Patient materials comprehension validation: To monitor the implementation of the BMS PPP. Drug utilisation studies as agreed with the NCA: To understand the demographics of the target population and number of women of child bearing potential.
Severe Infections (Sepsis, Septic Shock, and Viral Reactivation of Hepatitis B)	
Evidence for linking the risk to the medicine	Severe infections (eg, fatal sepsis including septic shock) have been observed following treatment with thalidomide in the postmarketing setting and can be life-threatening or fatal depending on the severity. Pneumonia is listed as a common event in Section 4.8 of the SmPC. Viral infections, including herpes zoster and hepatitis B virus (HBV) reactivation have been observed following treatment with thalidomide in the postmarketing setting (SmPC, Section 4.8).
Risk factors and risk groups	Numerous disease-related and chemotherapy-induced factors render the subject with cancer at increased risk for infection. These include the type of cancer, depth and duration of neutropenia, and impairments in cellular function caused by cytotoxic or immunosuppressive drugs; breaches in the integument from surgical procedures, presence of indwelling plastic venous catheters, or mucositis of the gastrointestinal tract secondary to chemotherapy; and comorbid conditions such as malnutrition, deconditioning, or medical problems such as chronic obstructive lung disease or diabetes. In addition, steroid therapy induces a broad immunosuppressive effect, including impaired chemotaxis and killing by neutrophils, impaired T-cell function, and alterations in skin and mucosal barriers. Long-term or high-dose steroid therapy is a significant risk factor for invasive fungal infections in particular; such therapy also may predispose affected subjects to development of bacterial infections and *Mycobacterium tuberculosis* reactivation. Iron overload and cigarette smoking are also risk factors for infection. Hepatitis B virus persists for decades in patients following recovery from acute HBV infection, during which it is controlled by the immune system. Therefore, situations that lead to immunosuppression in patients with chronic HBV infection may alter the natural history of this infection and give rise to reactivation. Risk factors for HBV reactivation include baseline HBV deoxyribonucleic acid (DNA) > 10^5 copies/mL, baseline alanine aminotransferase (ALT) levels, hepatitis B e antigen (HBeAg) seropositivity, corticosteroid therapy, anthracyclines, rituximab, male sex, younger age, and underlying disease of lymphoma or breast cancer.
Risk minimisation measures	**Routine Risk Minimisation Activities:** **SmPC** Section 4.4 where advice is given regarding the monitoring for severe infections Section 4.8 where severe infections are listed as ADRs. **PL** Advice to patients in PL, including a statement that the doctor is advised to check if the patient has ever had hepatitis B infection prior to starting thalidomide treatment. **Additional Risk Minimisation Activities:** Direct HCP communication distributed in all countries where thalidomide was marketed from Jun 2016 onwards to inform HCPs of the risk of viral reactivation.

Important identified risks

Additional pharmacovigilance activities	None
Acute Myeloid Leukaemia and Myelodysplastic Syndromes	
Evidence for linking the risk to the medicine	In clinical trials and postmarketing data, SPM have been reported in patients treated with thalidomide as well as with drugs in the same class. A statistically significant increase of AML and MDS has been observed in 1 clinical trial in patients with previously untreated MM receiving the combination of melphalan, prednisone, and thalidomide (MPT; SmPC, Section 4.4). Based on study MM-020, in patients receiving MPT, the haematologic SPM incidence rate (0.72 per 100 patient-years) was increased as compared to lenalidomide in combination with dexamethasone (0.17 per 100-patient-years).
Risk factors and risk groups	Travis has recently grouped second primary cancers into 3 major groups based on the predominant etiologic factors ie, treatment-related, syndromic, and those due to shared etiologic factors, while emphasising the nonexclusivity of these groups. Possible explanations for the epidemiologic findings presented in the previous section will be discussed below. • **Prolonged Survival as a Result of Improved Therapies** Due to improvements in the care of patients with cancer, the number of cancer survivors has been increasing in recent years. Increased longevity increases the risk of developing a second malignancy, whether due to the late sequelae of treatment, lifestyle factors, environmental exposures, or host factors (eg, aging, genetic factors, gene-environment interactions), or a combination of these factors. Second solid tumours are a leading cause of mortality among several populations of long-term survivors. Therapy-associated solid tumours are thought to be most commonly associated with radiotherapy, with a latency period typically greater than 10 years. Radiotherapy in the context of MM is most commonly employed in the treatment of solitary plasmocytomas and for palliation of skeletal lesions. As reported from the SEER Cancer Statistics Review 1975 to 2007, the 5-year relative survival (RS) among MM patients has increased from 26% among patients first diagnosed in 1975 to 1977 to 38% among patients first diagnosed between 1999 and 2006. Among patients aged less than 65 years at first diagnosis, 5-year RS is 50.6%; among those aged 65 years and older, survivorship is 28.1%. • **Exposure to Alkylating Agents** The risk of developing MDS and/or AML following the use of alkylating agents has been recognised for several decades and the risk may increase with increasing cumulative dose. The risk of AML begins to increase at 1 to 2 years, and peaks at 5 to 10 years followed by a decrease afterwards. In many cases there is a preceding MDS, including chromosomal abnormalities. Alkylating agents linked to human leukaemia include busulfan, carmustine, chlorambucil, cyclophosphamide, dihydroxybusulfan, lomustine, mechlorethamine, melphalan, prednimustine, and semustine. One of the best-characterised and most potent leukemogenic alkylating drugs is melphalan. • **Cytogenetic Markers** Interestingly, chromosomal anomalies of the same types that are seen in primary AML are seen in most cases of therapy-associated MDS or AML. Therapy-associated AML or MDS are well-recognised complications of therapy in MM patients. Significant transformation risk extends for many years following therapy.

Important identified risks

	Cytogenetic studies have identified specific karyotypes that are regularly associated with specific cytotoxic exposures, and these karyotypes have implications for both the development of MDS/AML and for survivorship. • **Lymphoproliferative Disorders in ASCT Patients** The development of post-transplant lymphoproliferative disorder (PTLD) after solid organ transplantation is well recognised. Most cases are due to Epstein-Barr Virus (EBV)-driven tumour formation in B cells. Other important risks include the use of potent and prolonged immunosuppressive medication, the age of donor (in the case of allogenic transplantation) and recipient, number and severity of rejection episodes and cytokine gene polymorphisms. In patients with MM a number of prospective, randomised trials have been conducted that compare conventional chemotherapy with high-dose therapy using autologous stem cell transplantation (ASCT). As a result of these studies, ASCT has nowadays become a standard of care in MM. However, these patients are at risk of developing PTLD. Reports have demonstrated that haematopoietic stem cell transplant patients with PTLD generally have higher concentrations of EBV DNA in the peripheral blood than patients without PTLD. • **Granulocyte Colony-stimulating Factor Therapy** Recent guidelines for cancer care support the use of G-CSF prophylaxis in specific therapeutic circumstances. Despite the usefulness of G-CSF therapy, increased risks of AML or MDS associated with G-CSF use have been described. Lyman recently provided a systematic review of AML/MDS incidence among 6058 and 6746 patients randomly assigned to receive chemotherapy with and without initial G-CSF support in 25 randomised clinical trials. At mean and median follow-up across studies of 60 and 53 months, respectively, AML/MDS was reported in 22 control patients and 43 G-CSF patients, for an estimated RR of 1.92 (95% CI: 1.19-3.07; p = 0.007). Median follow-up time was 54 months. The risk of AML/MDS was significantly increased in studies where G-CSF use was associated with higher total dose of chemotherapy (RR = 2.334; 95% CI: 1.237-4.403; p = 0.009). There was no significant difference in the RR for mortality. Even though these findings do not establish a unique causal role associated with the use of G-CSF the median follow-up of about 5 years may be insufficient to provide a final quantification of AML/MDS. • **Heredity** Additional insight has also been obtained in elucidating the risk of malignancies in close family members of patients affected by MM. The available data show an increased risk of more than 1 malignancy in MM patients and first degree relatives compared to the general population. The reason for this finding is still unclear but may clearly involve risk conferred by shared genetic factors.
Risk minimisation measures	**Routine Risk Minimisation Activities:** **SmPC** Section 4.4 which warns of the risk of AML and MDS with regard to benefit of thalidomide treatment and that patients should be carefully evaluated before and during treatment. Section 4.8 where AML/MDS are listed as ADRs. **PL** Advice to patients in PL regarding the possibility of developing AML and MDS. **Additional Risk Minimisation Activities:** Direct HCP communication distributed in all countries where thalidomide was marketed from Apr 2013 onwards.

Important identified risks

Additional pharmacovigilance activities	Long-term follow-up and solicited reporting for AML and MDS in clinical trials.

Important potential risks

Ischaemic Heart Disease (Including Myocardial Infarction)	
Evidence for linking the risk to the medicine	In clinical trials, events of myocardial infarction (MI) were reported more frequently in patients treated with thalidomide. Myocardial infarction has been reported in patients receiving thalidomide in the postmarketing setting, particularly in those with known risk factors (SmPC, Sections 4.4 and 4.8); Ischaemic heart disease, including MI, can be life-threatening or fatal depending on the severity, and can impact activities of daily living. Other cardiac events, such as Cardiac failure and bradycardia are listed as common events in Section 4.8 of the SmPC.
Risk factors and risk groups	In addition to advanced age, there are many established risk factors for MI, such as hereditary factors, male gender, smoking, diabetes mellitus, endstage renal disease and excessive dietary fat. Common comorbidities among MI patients aged 65 years and older include congestive heart failure, hypertension, and diabetes. Additional known risk factors include hypercholesterolemia and sedentary lifestyle. Furthermore MM is characterised by a proliferation of malignant plasma cells, and a subsequent overabundance of monoclonal paraprotein. The overproduction of these paraproteins may lead to hyperviscosity, amyloidosis, and renal failure. It has been suggested that hyperviscosity occasionally can lead to increased viscosity of the blood, resulting in complications such as stroke, myocardial ischaemia, or infarction.
Risk minimisation measures	**Routine Risk Minimisation Activities:** **SmPC** Section 4.2 which provides advice regarding prophylaxis for ischaemic heart disease Section 4.4 which warns of the risk factors for myocardial infarction Section 4.8 which lists myocardial infarction as an ADR. **PL** Advice to patients in PL regarding the risk of ischaemic heart disease. **Additional Risk Minimisation Activities:** Educational material for HCPs and patients
Additional pharmacovigilance activities	None

Other Second Primary Malignancies	
Evidence for linking the risk to the medicine	In clinical trials, other SPM has been recorded in some patients receiving thalidomide.
Risk factors and risk groups	Travis has recently grouped second primary cancers into 3 major groups based on the predominant etiologic factors ie, treatment-related, syndromic, and those due to shared etiologic factors, while emphasising the nonexclusivity of these groups. In the following,

Important potential risks

possible explanations for the epidemiologic findings presented in the previous section will be discussed.

- **Prolonged Survival as a Result of Improved Therapies**

Due to improvements in the care of patients with cancer, the number of cancer survivors has been increasing in recent years. Increased longevity increases the risk of developing a second malignancy, whether due to the late sequelae of treatment, lifestyle factors, environmental exposures, or host factors (eg, aging, genetic factors, gene-environment interactions), or a combination of these factors. Second solid tumours are a leading cause of mortality among several populations of long-term survivors. Therapy-associated solid tumours are thought to be most commonly associated with radiotherapy, with a latency period typically greater than 10 years. Radiotherapy in the context of MM is most commonly employed in the treatment of solitary plasmocytomas and for palliation of skeletal lesions.

As reported from the SEER Cancer Statistics Review 1975 to 2007, the 5-year RS among MM patients has increased from 26% among patients first diagnosed in 1975 to 1977 to 38% among patients first diagnosed between 1999 and 2006. Among patients aged less than 65 years at first diagnosis, 5-year RS is 50.6%; among those aged 65 years and older, survivorship is 28.1%.

- **Exposure to Alkylating Agents**

The risk of developing MDS and/or AML following the use of alkylating agents has been recognised for several decades and the risk may increase with increasing cumulative dose. The risk of AML begins to increase at 1 to 2 years, and peaks at 5 to 10 years followed by a decrease afterwards. In many cases there is a preceding MDS, including chromosomal abnormalities. Alkylating agents linked to human leukaemia include busulfan, carmustine, chlorambucil, cyclophosphamide, dihydroxybusulfan, lomustine, mechlorethamine, melphalan, prednimustine, and semustine. One of the best-characterised and most potent leukemogenic alkylating drugs is melphalan.

- **Cytogenetic Markers**

Interestingly, chromosomal anomalies of the same types that are seen in primary AML are seen in most cases of therapy-associated MDS or AML.

Therapy-associated AML or MDS are well-recognised complications of therapy in MM patients. Significant transformation risk extends for many years following therapy. Cytogenetic studies have identified specific karyotypes that are regularly associated with specific cytotoxic exposures, and these karyotypes have implications for both the development of MDS/AML and for survivorship.

- **Lymphoproliferative Disorders in ASCT Patients**

The development of PTLD after solid organ transplantation is well recognised. Most cases are due to EBV-driven tumour formation in B cells. Other important risks include the use of potent and prolonged immunosuppressive medication, the age of donor (in the case of allogenic transplantation) and recipient, number and severity of rejection episodes and cytokine gene polymorphisms. In patients with MM a number of prospective, randomised trials have been conducted that compare conventional chemotherapy with high-dose therapy using ASCT. As a result of these studies, ASCT has nowadays become a standard of care in MM. However, these patients are at risk of developing PTLD. Reports have demonstrated that haematopoietic stem cell transplant patients with PTLD generally have higher concentrations of EBV DNA in the peripheral blood than patients without PTLD.

- **Granulocyte Colony-stimulating Factor Therapy**

Recent guidelines for cancer care support the use of G-CSF prophylaxis in specific therapeutic circumstances. Despite the usefulness of G-CSF therapy, increased risks of AML or MDS associated with G-CSF use have been described. Lyman recently provided

Important potential risks

	a systematic review of AML/MDS incidence among 6058 and 6746 patients randomly assigned to receive chemotherapy with and without initial G-CSF support in 25 randomised clinical trials. At mean and median follow-up across studies of 60 and 53 months, respectively, AML/MDS was reported in 22 control patients and 43 G-CSF patients, for an estimated RR of 1.92 (95% CI: 1.19-3.07; p = 0.007). Median follow-up time was 54 months. The risk of AML/MDS was significantly increased in studies where G-CSF use was associated with higher total dose of chemotherapy (RR = 2.334; 95% CI: 1.237-4.403; p = 0.009). There was no significant difference in the RR for mortality. Even though these findings do not establish a unique causal role associated with the use of G-CSF the median follow-up of about 5 years may be insufficient to provide a final quantification of AML/MDS. • **Heredity** Additional insight has also been obtained in elucidating the risk of malignancies in close family members of patients affected by MM. The available data show an increased risk of more than 1 malignancy in MM patients and first degree relatives compared to the general population. The reason for this finding is still unclear but may clearly involve risk conferred by shared genetic factors.
Risk minimisation measures	**Routine Risk Minimisation Activities:** **SmPC** Section 4.4 where a warning is provided that other SPM, such as AML and MDS have been observed after thalidomide treatment **PL** Advice to patients in PL regarding the risk of SPM. **Additional Risk Minimisation Activities:** Direct Healthcare Professional Communication (DHPC) distributed in all countries where thalidomide was marketed from Apr 2013 onwards.
Additional pharmacovigilance activities	Long-term follow-up and solicited reporting for other SPM in clinical trials. Invasive SPM will be considered important medical events

Hepatic Disorders (Hepatocellular and Cholestatic Liver Injury)

Evidence for linking the risk to the medicine	In clinical trials, hepatic disorders were common events which were predominantly Grade 1 or 2 in severity. Hepatic disorders, mainly abnormal liver test results, have been reported following treatment with thalidomide in the postmarketing setting (SmPC, Sections 4.4 and 4.8) and may result in significant morbidity and mortality depending on the severity and may impact activities of daily living.
Risk factors and risk groups	Cancer chemotherapy may cause hepatic injury since drug effects may be cytotoxic for both normal and tumour cells. Recent reviews summarise current knowledge regarding hepatotoxicity associated with chemotherapeutic agents employed in the treatment of MM. Despite its being metabolised by the liver, adverse reactions associated with cyclophosphamide have only rarely been reported. Melphalan produces transient abnormalities in liver function tests at the high doses used in autologous BMT. Doxorubicin is extensively metabolised in the liver and an increased incidence of hepatotoxicity has been reported. Bortezomib is metabolised by the liver and hyperbilirubinemia and portal vein thrombosis have been reported. Hepatic disorders with thalidomide have been described in literature (see Safety Topic Review: Review of Hepatic Disorders in Patients Treated with Thalidomide, dated 05 Dec 2011). Hepatic adverse effects have also been associated with molecular-targeted cancer

Important potential risks

	treatments. Severe hepatitis has been described with the use of imatinib. Gemtuzumab and imatinib have been reported to induce autoimmune hepatitis. While MM predominantly affects bone marrow and bones, myelomatous infiltration of extraosseus tissues may occur in the reticuloendothelial system, including liver, spleen, and lymph nodes. Summarising cases of MM presenting at the Mayo Clinic between 1960 to 1971 and between 1985 to 1998, Kyle and colleagues noted that a palpable liver was present in 21% and 4% of patients at the time of initial diagnosis, respectively. Among 2584 patients treated at the Myeloma Institute for Research and Therapy from Aug 1997 to Nov 2003, 24 patients with gastrointestinal system involvement documented by tissue biopsy were identified. The organ mostly commonly involved was the liver (11 patients; 0.43%). These authors noted that gastrointestinal involvement at the time of initial diagnosis is much rarer than gastrointestinal involvement later in the course of the disease and that it often develops in patients with relapsing disease after SCT. Median survival after diagnosis of gastrointestinal involvement was 7 months (range, 1 to 54 months). Sixty-four necropsies of patients with MM were reviewed for liver diseases. Only 6 (9%) had a normal liver on histological examination; plasma cell infiltrates in the liver was noted in 56% of the patients and amyloidosis was reported in 6% to15% of patients with MM. Abnormalities of liver function tests were frequently noted and there was a relatively high incidence of jaundice.
Risk minimisation measures	**Routine Risk Minimisation Activities:** **SmPC** Section 4.4 where clinicians are advised to monitor patients for liver function. Section 4.8 where hepatic disorders are listed as ADRs. **PL** Advice to patients in PL regarding the risk of hepatic disorders. **Additional Risk Minimisation Activities:** None proposed.
Additional pharmacovigilance activities	None
Off-label Use	
Evidence for linking the risk to the medicine	There is potential for the use of thalidomide in indications other than the approved indications.
Risk factors and risk groups	Different target population with a potentially higher rate of women of childbearing potential exposed and the risk of teratogenicity.

Important potential risks

Risk minimisation measures	**Routine Risk Minimisation Activities:** – The SmPC details the risks associated with thalidomide use and actions to be taken in the event of specific AEs. – Advice to patients in PL. **Additional Risk Minimisation Activities:** – DHPC prior to launch. – Educational material for HCPs. – Agree with each Member State prior to the launch of the product the most appropriate strategies to monitor the off-label use within national territories.
Additional pharmacovigilance activities	Mechanisms for monitoring off-label use will be implemented as agreed with the NCA. This may include drug utilisation studies.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

None.

II.C.2 Other studies in post-authorisation development plan

Additional monitoring of implementation of Thalidomide BMS PPP on a country specific basis in accordance with local legal framework and with the agreement of the relevant NCA

Purpose of activity: To monitor the implementation of the BMS PPP on a country specific basis.

Patient materials comprehension validation

Purpose of activity: To monitor the implementation of the BMS PPP.

Implementation of NCA agreed mechanism for monitoring off-label use

Purpose of activity: To monitor off-label use.

Drug utilisation studies as agreed with the NCA

Purpose of activity: To understand the demographics of the target population and number of women of child bearing potential.

Long-term follow-up and solicited reporting of SPM in clinical trials

Purpose of activity: Long-term safety evaluation and monitoring of SPM in the context of clinical trials.

APPENDIX 1: REFERENCES

9 page(s) excluding cover page

APPENDIX 1: REFERENCES

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ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

48 page(s) excluding cover page

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

TABLE OF CONTENTS

Bristol Myers Squibb™
P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

Event-Specific Questionnaire for HCP – Pregnancy Background

(Patient or Partner of Patient)
Telephone: 1-800-721-5072
Fax: 609-818-3804
Email: Worldwide.Safety@BMS.com

Reporter Information			
REPORTER NAME:			
ADDRESS:		CITY, STATE, ZIP, COUNTRY:	
PHONE NO.:		FAX NO.:	
Obstetrician Information (Please provide)			
OBSTETRICIAN NAME:			
ADDRESS:		CITY, STATE, ZIP, COUNTRY:	
PHONE NO.:		FAX NO.:	
Patient Information			
PATIENT ID:	DATE OF BIRTH:	ETHNICITY: ☐ WHITE ☐ BLACK ☐ ASIAN ☐ OTHER, SPECIFY:	
Partner of Patient Information ☐ Not applicable			
DATE OF BIRTH:	ETHNICITY: ☐ WHITE ☐ BLACK ☐ ASIAN ☐ OTHER, SPECIFY:		
Patient Treatment Information: [DRUG NAME]®			
LOT NO.:	EXPIRY DATE:	DOSE:	FREQUENCY:
ROUTE:	START DATE:	STOP DATE:	
INDICATION FOR USE:			
CYTOGENETIC ABNORMALITIES: ☐ NO ☐ YES If Yes, specify:			

Current Pregnancy			
Date of Last Menstrual Period:		Estimated Delivery Date:	
PREGNANCY TEST	DATE	REFERENCE RANGE	RESULT
Urine qualitative			
Serum quantitative			
Prenatal Tests			
	DATE	RESULT	
Ultrasound			
Ultrasound			
Ultrasound			
Amniocentesis			
Maternal serum AFP			
Pregnancy History			
No. of previous pregnancies: Date of last pregnancy:	No. of full term births:	No. of preterm births:	
No. of fetal deaths:	No. of living children:	No. of abortions: Elective _____ Spontaneous _____	

Type of delivery: ☐ Vaginal ☐ C-section

Did birth defect occur in any previous pregnancy? ☐ No ☐ Yes ☐ Unknown

If Yes,
specify: _____

Did a stillbirth or spontaneous abortion occur in any previous pregnancy? ☐ No ☐ Yes ☐ Unknown

1) If Yes, in what week of pregnancy did the stillbirth or spontaneous abortion occur?
Week: _____

2) Was there any birth defect noted? ☐ No ☐ Yes, If Yes, specify: _____

Relevant Medical History

☐ NO ☐ YES IF YES, SPECIFY:

MEDICAL HISTORY	DATE OF DIAGNOSIS	MEDICAL HISTORY	DATE OF DIAGNOSIS

Social History

ALCOHOL USE ☐ NO ☐ YES, IF YES, AMOUNT/UNIT CONSUMED PER DAY:

TOBACCO USE ☐ NO ☐ YES	IV OR RECREATIONAL DRUG USE ☐ NO ☐ YES, IF YES, SPECIFY:

Family History: CONGENITAL ABNORMALITIES ☐ NO ☐ YES, IF YES, SPECIFY: _____

If there is a family history of congenital abnormalities, was there a consultation with a Geneticist?

☐ NO ☐ YES, IF YES, SPECIFY: _____

Environmental Exposure (e.g. RADIATION, CHEMICAL EXPOSURE) ☐ NO ☐ YES, IF YES, SPECIFY:

Medications/Treatments (including herbal, alternative and over-the-counter medicines and dietary supplements) During Pregnancy

MEDICATION/TREATMENT	START DATE	STOP DATE/ ONGOING	INDICATION

Adverse Event(s) During Pregnancy

EVENT(S)	ONSET DATE	STOP DATE / ONGOING	SERIOUS		CAUSAL RELATIONSHIP TO [DRUG NAME] ®	
			Y/N	SERIOUS CRITERIA[1]	Y/N	IF NO, WHAT MEDICATIONS, DISEASE STATES, etc, PLAYED A ROLE IN THE EVENT?

[1] Serious Criteria: **1**) death, **2**) life-threatening, **3**) required inpatient hospitalization or prolongation of existing hospitalization, **4**) a persistent or significant disability/incapacity, **5**) a congenital anomaly/birth defect, **6**) medically significant

Root Cause of Pregnancy

1. What forms of birth control was your patient using while on [Drug Name] before becoming pregnant or impregnating their partner? Please check all that apply.

Tubal ligation	☐ Yes	☐ No
IUD	☐ Yes	☐ No
Hormonal birth control	☐ Yes	☐ No
Partner's vasectomy	☐ Yes	☐ No
Male latex or synthetic condom	☐ Yes	☐ No
Diaphragm	☐ Yes	☐ No
Cervical cap or shield	☐ Yes	☐ No
Spermicide or sponge	☐ Yes	☐ No
Withdrawal	☐ Yes	☐ No
Abstinence	☐ Yes	☐ No

2. Was your patient or their partner without contraception for even one day at any time during use of [DRUG NAME]®**?**

☐ No, please proceed to Question 5

☐ Yes, please answer Question 3, Question 4, Question 5, and Question 6

3. If applicable per Question 2, how often did your patient have unprotected sexual intercourse?

☐ Multiple times

☐ Once a week

☐ Once every 2 weeks

☐ Once a month

☐ Not at all

☐ Other, specify _____

4. If applicable per Question 2, why did your patient and/or their partner interrupt or stop using contraception?

☐ Wanted a child

¨ Partner disapproved

☐ Side effects

☐ Health concerns

☐ Inconvenient to use

☐ Other, specify _____

5. Please ask your patient if they received the [Drug Name]® Patient Information (e.g. Medication Guide or patient leaflet).

☐ No, please proceed to Question 5.3

☐ Yes, please answer Question 5.1

5.1 Please ask your patient if they read the [Drug Name]® Patient Information (e.g. Medication Guide or patient leaflet).

☐ No, please proceed to Question 5.3

☐ Yes, please answer Question 5.2

5.2 Please ask your patient if they understood the information in the [Drug Name]® Patient Information (e.g. Medication Guide or patient leaflet).

☐ No, please proceed to Question 5.3

☐ Yes, please proceed to Question 5.3

5.3 Please ask your patient where most of their knowledge about contraception during [Drug Name]® use came from.

☐ Physician who prescribed [Drug Name]®

☐ Patient Guide to the [Drug Name] REMS® Program

☐ [Drug Name]® Patient Information (e.g. Medication Guide or patient leaflet)

☐ Other, specify: _____

6. Please ask your patient if they felt that they and their partner had a good understanding of the risk of pregnancy during [Drug Name]® use.

☐ No

☐ Yes

☐ Don't know

SIGNATURE OF PERSON COMPLETING THIS FORM: _____ **DATE:** _____

MCN:

Bristol Myers Squibb™
P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

Event-Specific Questionnaire for HCP – Pregnancy Follow-up
(Patient or Partner of Patient)
Telephone: 1-800-721-5072
Fax: 609-818-3804
Email: Worldwide.Safety@BMS.com

Date:	**Period Covered:** _____ (Date) to _____ (Date)	
Reporter Information		
REPORTER NAME:		
ADDRESS:	CITY, STATE, ZIP, COUNTRY:	
PHONE NO.:	FAX NO.:	
Name of Patient or Pregnant Partner of Male Patient:		
Current Pregnancy		
Prenatal Tests (If any additional medical records relating to these prenatal tests are available, please attach along with this form)		
TEST	DATE	RESULT
Ultrasound		
Ultrasound		
Ultrasound		
Amniocentesis		
Maternal Serum AFP		
Other Tests, Specify:		
Pregnancy Type ☐ SINGLETON ☐ TWIN ☐ TRIPLET ☐ OTHER, SPECIFY: _____		

Medications/Treatments (including herbal, alternative and over-the-counter medicines and dietary supplements) During Pregnancy

MEDICATION/TREATMENT	START DATE	STOP DATE/ CONTINUING	INDICATION

Adverse Event(s) During Pregnancy

EVENT(S)	ONSET DATE	STOP DATE / ONGOING	SERIOUS		CAUSAL RELATIONSHIP TO [Drug Name] ®	
			Y/N	SERIOUS CRITERIA[1]	Y/N	IF NO, WHAT MEDICATIONS, DISEASE STATES, etc., PLAYED A ROLE IN THE EVENT?

[1] Serious Criteria: **1**) death, **2**) life-threatening, **3**) required inpatient hospitalization or prolongation of existing hospitalization, **4**) a persistent or significant disability/incapacity, **5**) a congenital anomaly/birth defect, **6**) medically significant

DATE:

SIGNATURE OF PERSON COMPLETING THIS FORM: _____ _____

MCN:

Bristol Myers Squibb™
P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

Event-Specific Questionnaire for HCP – Pregnancy Follow-up
(Patient or Partner of Patient)
Telephone: 1-800-721-5072
Fax: 609-818-3804
Email: Worldwide.Safety@BMS.com

Date:	**Period Covered:** _____ (Date) to _____ (Date)
Reporter Information	
REPORTER NAME:	
ADDRESS:	CITY, STATE, ZIP, COUNTRY:
PHONE NO.:	FAX NO.:
Name of Patient or Pregnant Partner of Male Patient:	
Current Pregnancy	

Prenatal Tests (If any additional medical records relating to these prenatal tests are available, please attach along with this form)

TEST	DATE	RESULT
Ultrasound		
Ultrasound		
Ultrasound		
Amniocentesis		
Maternal Serum AFP		
Other Tests, Specify:		

Pregnancy Type

☐ SINGLETON ☐ TWIN ☐ TRIPLET ☐ OTHER, SPECIFY: _____

Medications/Treatments (including herbal, alternative and over-the-counter medicines and dietary supplements) During Pregnancy

MEDICATION/TREATMENT	START DATE	STOP DATE/ CONTINUING	INDICATION

Adverse Event(s) During Pregnancy

EVENT(S)	ONSET DATE	STOP DATE / ONGOING	SERIOUS		CAUSAL RELATIONSHIP TO [Drug Name] ®	
			Y/N	SERIOUS CRITERIA[1]	Y/N	IF NO, WHAT MEDICATIONS, DISEASE STATES, etc., PLAYED A ROLE IN THE EVENT?

[1] Serious Criteria: **1**) death, **2**) life-threatening, **3**) required inpatient hospitalization or prolongation of existing hospitalization, **4**) a persistent or significant disability/incapacity, **5**) a congenital anomaly/birth defect, **6**) medically significant

DATE:

SIGNATURE OF PERSON COMPLETING THIS FORM: _____ _____

MCN:

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Event-Specific Questionnaire for HCP – Pregnancy Follow-up
(Patient or Partner of Patient)
Telephone: 1-800-721-5072
Fax: 609-818-3804
Email: Worldwide.Safety@BMS.com

Date:	**Period Covered:** _____ to _____ Date Date
Reporter Information	
REPORTER NAME:	
ADDRESS:	CITY, STATE, ZIP, COUNTRY:
PHONE NO.:	FAX NO.:
Name of Patient or Pregnant Partner of Male Patient:	
Current Pregnancy	
Prenatal Tests (If any additional medical records relating to these prenatal tests are available, please attach along with this form)	

TEST	DATE	RESULT
Ultrasound		
Ultrasound		
Ultrasound		
Amniocentesis		
Maternal Serum AFP		
Other Tests, Specify:		

Pregnancy Type

☐ SINGLETON ☐ TWIN ☐ TRIPLET ☐ OTHER, SPECIFY: _____

Medications/Treatments (including herbal, alternative and over-the-counter medicines and dietary supplements) During Pregnancy

MEDICATION/TREATMENT	START DATE	STOP DATE/ CONTINUING	INDICATION

Adverse Event(s) During Pregnancy

EVENT(S)	ONSET DATE	STOP DATE / ONGOING	SERIOUS		CAUSAL RELATIONSHIP TO [Drug Name] ®	
			Y/N	SERIOUS CRITERIA[1]	Y/N	IF NO, WHAT MEDICATIONS, DISEASE STATES, etc., PLAYED A ROLE IN THE EVENT?

[1] Serious Criteria: **1**) death, **2**) life-threatening, **3**) required inpatient hospitalization or prolongation of existing hospitalization, **4**) a persistent or significant disability/incapacity, **5**) a congenital anomaly/birth defect, **6**) medically significant

SIGNATURE OF PERSON COMPLETING THIS FORM: _____ **DATE:** _____

MCN:

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Event-Specific Questionnaire for HCP – Pregnancy Outcome
(Patient or Partner of Patient)
Telephone: 1-800-721-5072
Fax: 609-818-3804
Email: Worldwide.Safety@BMS.com

Reporter Information			
REPORTER NAME:			
ADDRESS:		CITY, STATE, ZIP, COUNTRY:	
PHONE NO.:		FAX NO.:	
Patient Information			
PATIENT ID:	DATE OF BIRTH:	ETHNICITY: ☐ WHITE ☐ BLACK ☐ ASIAN ☐ OTHER, SPECIFY:	
Partner of Patient Information ☐ Not applicable			
DATE OF BIRTH:	ETHNICITY: ☐ WHITE ☐ BLACK ☐ ASIAN ☐ OTHER, SPECIFY:		
Pregnancy Type ☐ SINGLETON ☐ TWIN ☐ TRIPLET ☐ OTHER, SPECIFY: _____			
Pregnancy Outcome			
DATE OF DELIVERY:			GESTATION AGE AT DELIVERY:
DELIVERY DETAILS	NO	YES	ADDITIONAL COMMENTS
Normal	☐	☐	
C-section	☐	☐	
Induced	☐	☐	
Assisted (e.g., forceps)	☐	☐	
Elective Termination	☐	☐	Date:
Spontaneous Abortion (≤ 20 weeks)	☐	☐	Weeks from LMP:
Fetal Death/Stillbirth (> 20 weeks)	☐	☐	
Were the Products of Conception Examined?	☐	☐	If yes, was the fetus normal? ☐ Yes ☐ No ☐ Unknown If no, describe: _____

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Obstetrics Information			
	NO	YES	
Complications During Pregnancy	☐	☐	If Yes, specify:
Complications During Labor/Delivery	☐	☐	If Yes, specify:
Post-partum Maternal Complications	☐	☐	If Yes, specify:
Fetal and Neonatal Status			
	NO	YES	
Live Normal Infant	☐	☐	
Fetal Distress	☐	☐	If Yes, specify:
Intra-uterine Growth Retardation	☐	☐	If Yes, specify:
Neonatal Complications*	☐	☐	If Yes, specify:
Birth Defect Noted?	☐	☐	If Yes, specify:

Sex: ☐ Male ☐ Female **Birth Weight:** ___ lbs ___ oz ***or*** ___ kg **Length:** ___ inches ***or*** ___ cm

Apgar Score:	Unknown:	1 min:	5 mins:	10 mins:

***PLEASE PROVIDE A BRIEF SUMMARY OF THE MANAGEMENT OF THE COMPLICATIONS.**

SIGNATURE OF PERSON COMPLETING THIS FORM: _____ **DATE:** _____

MCN:

Bristol Myers Squibb™
P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

Event-Specific Questionnaire for Primary Care Physician or Pediatrician – Infant Follow-up

Telephone: 1-800-721-5072
Fax: 609-818-3804
Email: Worldwide.Safety@BMS.com

Date of Assessment: _____

Age in Months: _____

Weight (at the time of this assessment): _____ lbs _____ oz ***or*** _____ kg

Length (at the time of this assessment): _____ inches ***or*** _____ cm

Name of Patient on [Drug Name]®: _____

Name of Infant (if known): _____

Please provide information for the period from _____ Date to _____ Date

Birth Defects/Anomalies:

New birth defects or anomalies noted since previous report? ☐ Yes ☐ No

If **Yes**, please list the birth defects/anomalies below:

BIRTH DEFECT/ANOMALY	**WAS THE DEFECT/ ANOMALY ATTRIBUTED TO [Drug Name]® THERAPY?** (Y/N/UNKNOWN)	**FACTORS THAT MAY HAVE CONTRIBUTED TO THIS OUTCOME:** (e.g. FAMILY HISTORY, MATERNAL AGE, OBESITY, ALCOHOL CONSUMPTION DURING PREGNANCY, etc.)	**DEFECT/ ANOMALY NOTED PRIOR TO BIRTH?** (Y/N)	**INFANT AGE WHEN DEFECT/ ANOMALY WAS NOTED** (SPECIFY WEEKS OR MONTHS)

Developmental Assessment:

Is the child developing normally for his/her age? ☐ Yes ☐ No

If No, please define your concerns regarding any developmental issues or abnormalities:

Diagnosis date of any developmental issues: _____

Infant Illnesses, Hospitalizations, Drug Therapies:

Infant Illnesses	Hospitalized?	Drug Therapies
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	

SIGNATURE OF PERSON COMPLETING THIS FORM: _____ **DATE:** _____

MCN:

Bristol Myers Squibb™
P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

Event-Specific Questionnaire for Primary Care Physician or Pediatrician – Infant Follow-up

Telephone: 1-800-721-5072
Fax: 609-818-3804
Email: Worldwide.Safety@BMS.com

Date of Assessment: _____

Age in Months: _____

Weight (at the time of this assessment): _____ lbs _____ oz ***or*** _____ kg

Length (at the time of this assessment): _____ inches ***or*** _____ cm

Name of Patient on [Drug Name]®: _____

Name of Infant (if known): _____

Please provide information for the period from _____ Date to _____ Date

Birth Defects/Anomalies:

New birth defects or anomalies noted since previous report? ☐ Yes ☐ No

If **Yes**, please list the birth defects/anomalies below:

BIRTH DEFECT/ANOMALY	**WAS THE DEFECT/ ANOMALY ATTRIBUTED TO [Drug Name] ® THERAPY?** (Y/N/UNKNOWN)	**FACTORS THAT MAY HAVE CONTRIBUTED TO THIS OUTCOME:** (e.g. FAMILY HISTORY, MATERNAL AGE, OBESITY, ALCOHOL CONSUMPTION DURING PREGNANCY, etc.)	**DEFECT/ ANOMALY NOTED PRIOR TO BIRTH?** (Y/N)	**INFANT AGE WHEN DEFECT/ ANOMALY WAS NOTED** (SPECIFY WEEKS OR MONTHS)

Developmental Assessment:

Is the child developing normally for his/her age? ☐ Yes ☐ No

If No, please define your concerns regarding any developmental issues or abnormalities:

Diagnosis date of any developmental issues: _____

Infant Illnesses, Hospitalizations, Drug Therapies:

Infant Illnesses	Hospitalized?	Drug Therapies
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	

SIGNATURE OF PERSON COMPLETING THIS FORM: _____ **DATE:** _____

MCN:

Bristol Myers Squibb™
P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

Event-Specific Questionnaire for Primary Care Physician or Pediatrician – Infant Follow-up

Telephone: 1-800-721-5072
Fax: 609-818-3804
Email: Worldwide.Safety@BMS.com

Date of Assessment: _____

Age in Months: _____

Weight (at the time of this assessment): _____ lbs _____ oz ***or*** _____ kg

Length (at the time of this assessment): _____ inches ***or*** _____ cm

Name of Patient on [Drug Name]®: _____

Name of Infant (if known): _____

Please provide information for the period from _____ Date to _____ Date

Birth Defects/Anomalies:

New birth defects or anomalies noted since previous report? ☐ Yes ☐ No

If **Yes**, please list the birth defects/anomalies below:

BIRTH DEFECT/ANOMALY	**WAS THE DEFECT/ ANOMALY ATTRIBUTED TO [Drug Name]® THERAPY?** (Y/N/UNKNOWN)	**FACTORS THAT MAY HAVE CONTRIBUTED TO THIS OUTCOME:** (e.g., FAMILY HISTORY, MATERNAL AGE, OBESITY, ALCOHOL CONSUMPTION DURING PREGNANCY, etc.)	**DEFECT/ ANOMALY NOTED PRIOR TO BIRTH?** (Y/N)	**INFANT AGE WHEN DEFECT/ ANOMALY WAS NOTED** (SPECIFY WEEKS OR MONTHS)

Developmental Assessment:

Is the child developing normally for his/her age? ☐ Yes ☐ No

If No, please define your concerns regarding any developmental issues or abnormalities:

Diagnosis date of any developmental issues: _____

Infant Illnesses, Hospitalizations, Drug Therapies:

Infant Illnesses	Hospitalized?	Drug Therapies
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	

SIGNATURE OF PERSON COMPLETING THIS FORM: _____ **DATE:** _____

MCN:

Bristol Myers Squibb™
P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

Event-Specific Questionnaire for Primary Care Physician or Pediatrician – Infant Follow-up

Telephone: 1-800-721-5072
Fax: 609-818-3804
Email: Worldwide.Safety@BMS.com

Date of Assessment: _____

Age in Months: _____

Weight (at the time of this assessment): _____ lbs _____ oz ***or*** _____ kg

Length (at the time of this assessment): _____ inches ***or*** _____ cm

Name of Patient on [Drug Name]®: _____

Name of Infant (if known): _____

Please provide information for the period from _____ Date to _____ Date

Birth Defects/Anomalies:

New birth defects or anomalies noted since previous report? ☐ Yes ☐ No

If **Yes**, please list the birth defects/anomalies below:

BIRTH DEFECT/ANOMALY	**WAS THE DEFECT/ ANOMALY ATTRIBUTED TO [Drug Name]® THERAPY?** (Y/N/UNKNOWN)	**FACTORS THAT MAY HAVE CONTRIBUTED TO THIS OUTCOME:** (e.g., FAMILY HISTORY, MATERNAL AGE, OBESITY, ALCOHOL CONSUMPTION DURING PREGNANCY, etc.)	**DEFECT/ ANOMALY NOTED PRIOR TO BIRTH?** (Y/N)	**INFANT AGE WHEN DEFECT/ ANOMALY WAS NOTED** (SPECIFY WEEKS OR MONTHS)

Developmental Assessment:

Is the child developing normally for his/her age? ☐ Yes ☐ No

If No, please define your concerns regarding any developmental issues or abnormalities:

Diagnosis date of any developmental issues: _____

Infant Illnesses, Hospitalizations, Drug Therapies:

Infant Illnesses	Hospitalized?	Drug Therapies
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	

SIGNATURE OF PERSON COMPLETING THIS FORM: _____ **DATE:** _____

MCN:

Bristol Myers Squibb™
P.O BOX 4000, B.3140
Princeton, NJ-08543-4000

[Case_ ID]

Adverse Event Report Questionnaire
TL Acute Myeloid Leukaemia AML or MDS in Non-MDS Indication Thalidomide Revlimid

INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:

Patient Demographics:

Patient's date of birth (DD-MMM-YYYY): _____ Gender: ☐ Male ☐ Female

Age: _____.

Race/Ethnicity: _____ ☐ Aborginal ☐ African American ☐ Asian
☐ American Indian or Alaskan Native ☐ Native Hawaiian or other Pacific Islander
☐ Torres Strait Islander ☐ White ☐ Black ☐ Non Hispanic

Age Group:_____

Note: Please provide Age Group if Patient's Date of Birth or Age is not available.

Age Group Definition: Neonate: 0 - 27 days, Infant: 28 days to 23 months, Child: 2 years to 11years, Adolescent: 12 years to 18 years, Adult: More than 18 years and less than or equal to 65 years and Elderly: equal or greater than 66 years)

Suspect Products: Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

	Suspect Product #1	Suspect Product #2	Suspect Product #3
Product name			
Daily dose and regimen			
Route of administration			
Indication			
Start date or treatment duration (DD-MMM-YYYY)			
Stop date (DD-MMM-YYYY)			
Lot/Batch number(s)			
Expiration date(s)			
Action Taken with the suspect product			

(Choose from one of the following for action Taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown)

Adverse Event (AE) Description: Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

	Adverse Event #1	Adverse Event #2	Adverse Event #3	Adverse Event #4

Add Diagnosis Here →				
Start Date (DD/MMM/YYYY)				
Stop Date (DD/MMM/YYYY)				
Time lag if AE occurred after cessation of treatment with the suspect product(s):				
Required Hospitalization (Yes/No)				
Life-Threatening (Yes/No)				
Persistent or significant disability (Yes/No)				
Congenital abnormality (Yes/No)				
Cause of Death (Yes/No)				
Treatment of Adverse Event				
Outcome (recovery and sequelae, if any)				
Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No)				
Did the event recur after reintroducing (Yes/No)				

Please summarize course of reported events including signs and symptoms in chronological order:

_____

_____

_____

Diagnostic tests (use additional pages if needed)**:** Please indicate test unit where applicable.

Date	Test Name	Pre-treatment value	AE onset value	AE resolution value	Normal low	Normal high

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

_____

_____

Concomitant Medications (use additional pages if needed)**:**

Did the Patient take any concomitant medication? ☐ Yes (please complete below) ☐ No ☐ Unknown
Please include all concomitant medications including indications, therapy dates and dosing information. These should include concurrent anti-myeloma therapy, colony-stimulating factors, and/or ESAs.

Medication Name	Daily dose and regimen	Route of administration	Indication	Start date DD-MMM-YYYY	Stop date DD-MMM-YYYY

Other Etiological Factors: ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical and/or drug history (please specify), including start date or duration:
Please include familial history of malignancies, environmental exposure, blood transfusion dependence status.

_____

_____

_____

☐ Family history (please specify): _____
☐ Drug/alcohol/tobacco abuse: _____
☐ Other (please specify): _____

Additional questions:

Please provide the date [Revlimid/Thalidomide drug indication, e.g., AML or MDS] was initially diagnosed with stage/classification.

Please provide full bone marrow results as well as full cytogenetics at baseline and at the time of diagnosis of [MDS or AML] with dates. Please specify if this information is not available or not evaluable.

Please specify AML type if not included in the bone marrow or cytogenetics documents. Please specify if this information is not available or not evaluable.

Please also provide the [Revlimid/Thalidomide indication] stage/classification at the time of the MDS or AML diagnosis. Please specify if this information is not available or not evaluable. Is there evidence of progression of underlying disease? Please explain.

Please provide changes in transfusion dependence status during disease (Revlimid/Thalidomide indication) treatment with corresponding dates.

Please provide information on any antineoplastic treatments the patient may have received including radiotherapy with radiation zone for any malignant neoplasm, specifying the indication for this. Please provide duration of treatment with dates and also cumulative dose if available.

Please specify what treatment was received for the AML/MDS.

What was the outcome of AML/MDS? If fatal outcome, please provide circumstances surrounding the death.

_____

Health Practitioner Name (Print)

_____

Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

Bristol Myers Squibb™
P.O BOX 4000, B.3140
Princeton, NJ-08543-4000

[Case_ ID]

Adverse Event Report Questionnaire
TL Myocardial infarction (Thalidomide_Revlimid)

INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:

Patient Demographics:

Patient's date of birth (DD-MMM-YYYY): _____ Gender: ☐ Male ☐ Female

Age: _____.

Race/Ethnicity: _____ ☐ Aborginal ☐ African American ☐ Asian
☐ American Indian or Alaskan Native ☐ Native Hawaiian or other Pacific Islander
☐ Torres Strait Islander ☐ White ☐ Black ☐ Non Hispanic

Age Group:_____

Note: Please provide Age Group if Patient's Date of Birth or Age is not available.

Age Group Definition: Neonate: 0 - 27 days, Infant: 28 days to 23 months, Child: 2 years to 11years, Adolescent: 12 years to 18 years, Adult: More than 18 years and less than or equal to 65 years and Elderly: equal or greater than 66 years)

Suspect Products: Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

	Suspect Product #1	Suspect Product #2	Suspect Product #3
Product name			
Daily dose and regimen			
Route of administration			
Indication			
Start date or treatment duration (DD-MMM-YYYY)			
Stop date (DD-MMM-YYYY)			
Lot/Batch number(s)			
Expiration date(s)			
Action Taken with the suspect product			

(Choose from one of the following for action Taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown)

Adverse Event (AE) Description: Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

	Adverse Event #1	Adverse Event #2	Adverse Event #3	Adverse Event #4

Add Diagnosis Here →				
Start Date (DD/MMM/YYYY)				
Stop Date (DD/MMM/YYYY)				
Time lag if AE occurred after cessation of treatment with the suspect product(s):				
Required Hospitalization (Yes/No)				
Life-Threatening (Yes/No)				
Persistent or significant disability (Yes/No)				
Congenital abnormality (Yes/No)				
Cause of Death (Yes/No)				
Treatment of Adverse Event				
Outcome (recovery and sequelae, if any)				
Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No)				
Did the event recur after reintroducing (Yes/No)				

Please summarize course of reported events including signs and symptoms in chronological order:

_____

_____

_____

Diagnostic tests (use additional pages if needed)**:** Please indicate test unit where applicable.

Date	Test Name	Pre-treatment value	AE onset value	AE resolution value	Normal low	Normal high
	CPK					
	MB					
	Troponin					
	BNP					
	WBC					
	ANC					
	RBC					
	Hgb					
	Hct					
	Magnesium					
	Calcium					

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

_____

Concomitant Medications (use additional pages if needed)**:**

Did the Patient take any concomitant medication? ☐ Yes (please complete below) ☐ No ☐ Unknown
Please include erythropoietin and thromboprophylactic medications and others as appropriate.

Medication Name	Daily dose and regimen	Route of administration	Indication	Start date DD-MMM-YYYY	Stop date DD-MMM-YYYY

Other Etiological Factors: ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical and/or drug history (please specify), including start date or duration:

☐ Family history (please specify): _____
☐ Drug/alcohol/tobacco abuse: _____
☐ Other (please specify): _____

Additional questions:

Did the patient have a history of cardiac disease such as coronary artery disease, myocardial infarction, arrhythmia, or congestive heart failure? Please provide the onset dates of diagnosis.

Please provide any risk factors for the myocardial infarction. (hyperlipidemia, hypercholesterolemia, obesity, hypertension, COPD, renal disease, diabetes, sepsis, substance abuse, sedentary life style, immobility, dehydration, etc.).

Please provide the following diagnostic results including the baseline and the most recent EKG, echocardiogram, stress test, and cardiac catheterization, if available.

Please provide the treatment and interventions that were administered due to the myocardial infarction.

Please provide concurrent events/circumstances surrounding the MI.

Did the patient have a history of chest pain?

Did the patient have a history of thromboembolic events? If yes, please specify type.

Health Practitioner Name (Print)

Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

Bristol Myers Squibb™
P.O BOX 4000, B.3140
Princeton, NJ-08543-4000

[Case_ ID]

Adverse Event Report Questionnaire
TL Second Primary Malignancies (Pomalyst Revlimid Thalidomide)

INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:

Patient Demographics:

Patient's date of birth (DD-MMM-YYYY): _____ Gender: ☐Male ☐ Female
Age: _____.

Race/Ethnicity: _____ ☐ Aborginal ☐African American ☐ Asian
☐ American Indian or Alaskan Native ☐ Native Hawaiian or other Pacific Islander
☐ Torres Strait Islander ☐ White ☐ Black ☐ Non Hispanic

Age Group:_____

Note: Please provide Age Group if Patient's Date of Birth or Age is not available.

Age Group Definition: Neonate: 0 - 27 days, Infant: 28 days to 23 months, Child: 2 years to 11years, Adolescent: 12 years to 18 years, Adult: More than 18 years and less than or equal to 65 years and Elderly: equal or greater than 66 years)

Suspect Products: Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

	Suspect Product #1	Suspect Product #2	Suspect Product #3
Product name			
Daily dose and regimen			
Route of administration			
Indication			
Start date or treatment duration (DD-MMM-YYYY)			
Stop date (DD-MMM-YYYY)			
Lot/Batch number(s)			
Expiration date(s)			
Action Taken with the suspect product			

(Choose from one of the following for action Taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown)

Adverse Event (AE) Description: Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

	Adverse Event #1	Adverse Event #2	Adverse Event #3	Adverse Event #4

Add Diagnosis Here →				
Start Date (DD/MMM/YYYY)				
Stop Date (DD/MMM/YYYY)				
Time lag if AE occurred after cessation of treatment with the suspect product(s):				
Required Hospitalization (Yes/No)				
Life-Threatening (Yes/No)				
Persistent or significant disability (Yes/No)				
Congenital abnormality (Yes/No)				
Cause of Death (Yes/No)				
Treatment of Adverse Event				
Outcome (recovery and sequelae, if any)				
Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No)				
Did the event recur after reintroducing (Yes/No)				

Please summarize course of reported events including signs and symptoms in chronological order:

_____

_____

_____

Diagnostic tests (use additional pages if needed)**:** Please indicate test unit where applicable.

Date	Test Name	Pre-treatment value	AE onset value	AE resolution value	Normal low	Normal high
	Calcium					
	Phosphate					
	Uric Acid					
	Creatinine					
	Potassium					
	LDH					
	Albumin					
	Protein					

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

_____

_____

Concomitant Medications (use additional pages if needed)**:**

Did the Patient take any concomitant medication? ☐ Yes (please complete below) ☐ No ☐ Unknown

Please include drugs that are potentially nephrotoxic (NSAIDS, antibiotics) including over the counter drugs.

Medication Name	Daily dose and	Route of	Indication	Start date	Stop date

	regimen	administration		DD-MMM-YYYY	DD-MMM-YYYY

Other Etiological Factors: ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical history (including history of malignancies) and/or drug history (please specify), including start date or duration:

_____

_____

_____

☐ Family history (please specify), including history of malignancies with estimated dates: _____
☐ Drug/alcohol/tobacco abuse: _____
☐ Other (please specify): _____

Additional questions:

When querying about SPMs, specify the malignancy or diagnosis. Do not use the term SPM when diagnosis is known.

Core Questions for Follow-up of SPMs:

1. Dates of the underlying disease's diagnosis.
2. Date of first clinical symptoms of SPM.
3. Stage of the underlying disease treated with [*BMS product*] at baseline, the end of treatment if applicable, and at the time of the event with supportive documentation if available.
4. Medical history of bone marrow transplant including dates, type, donor details, source, and conditioning regimens such as treatment with alkylating agents (i.e. Cyclophosphamide, Melphalan, etc.).
5. Environmental exposure e.g. atmospheric pollutants/toxic chemicals (pesticides, herbicides, benzene, solvents); occupation/hobbies.
6. Full SPM (*specify malignancy or diagnosis if known*) biopsy reports. If not available please provide the detailed results.

In addition to the Core Questions, specific information should be requested based on the risk factors for individual types of cancer, including:

Hematologic Malignancies (including Lymphoma and B-cell malignancy):

- ◊ Previous chemotherapy rounds (dates, type) and /or radiotherapy (zone, duration, cumulative dose) or subsequent ones if SPM (specify malignancy or diagnosis) detected after product discontinuation
- ◊ Medical conditions that compromise the immune system – HIV/AIDS, autoimmune diseases, diseases requiring immune suppressive therapy-organ transplant
- ◊ For lymphoma: Infection with HIV, Epstein-Barr virus+++, Helicobacter pylori, hepatitis B or C, human T-lymphotrophic virus type I, Burkitt's lymphoma

- Concurrent or medical/family history of inherited syndromes with genetic changes that raise the risk of acute lymphocytic leukemia (ALL) including: Down syndrome, Klinefelter syndrome, Fanconi anemia, Bloom syndrome, Ataxia-telangiectasia, Neurofibromatosis.
- Exposure to benzene (solvent used in the rubber industry, oil refineries, chemical plants, shoe manufacturing, and gasoline-related industries, and is also present in cigarette smoke, as well as some glues, cleaning products, detergents, art supplies, and paint strippers).
- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting
- Exposure to high levels of radiation
- Medical history of treated hematologic malignancies or concurrent leukemias or lymphomas including: Chronic Lymphocytic Leukemia (CLL), Richter transformation, and Diffuse Large B-cell lymphoma (DLBCL) such as Hodgkin's disease and plasmablastic lymphoma.
- Relevant diagnostic test results (if available), including: biopsy, immunohistochemistry, flow cytometry, cytogenetics, reverse transcriptase polymerase chain reaction, Fluorescence in situ hybridization (FISH), and next generation sequencing

Lung Cancer:

- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting
- Pre-existing pulmonary disease
- Family history of lung cancer

Thyroid Cancer:

- Personal or family history of thyroid and/or autoimmune diseases – hypo or hyperthyroidism, goiter, benign thyroid nodules, Hashimoto's disease, Graves disease
- Family history of familial medullary thyroid cancer, multiple endocrine neoplasia and familial adenomatous polyposis
- Living in iodine deficient area
- History of radiation exposure

Breast Cancer:

- Receptor status of the tumor – ER, PR, Her2/neu
- Age at onset of menses and age of menopause
- Number of pregnancies and age at first birth
- History of breastfeeding children
- Use of oral contraceptives or hormone replacement therapy
- Obesity
- Economic status, and dietary iodine deficiency

Ovarian Cancer:

- Number of pregnancies and childbearing status
- History of hormone replacement therapy
- History of breast cancer

Uterine Cancer:

- Age at onset of menses and age of menopause
- Number of pregnancies
- Use of oral contraceptives
- Obesity

Colon Cancer:

- ◊ Family or personal history of adenomatous polyposis (FAP), Lynch syndrome (Hereditary nonpolyposis colorectal cancer)
- ◊ Diet high in red meat and animal fat, refined carbohydrates, low-fiber diet, and low overall intake of fruits and vegetables
- ◊ Obesity and sedentary habits
- ◊ Any history of inflammatory conditions of digestive tract - Chronic ulcerative colitis, Crohn's disease longer duration, greater extent of colon involvement

Anorectal Cancer:

- ◊ History of infection with human papillomavirus, HIV, chronic fistulas, irradiated anal skin, leukoplakia, lymphogranulomatoma venereum, condyloma acuminatum

Gastric Cancer:

- ◊ Diet rich in pickled vegetables, salted fish, salt, and smoked meats
- ◊ Helicobacter pylori infection
- ◊ Obesity
- ◊ Previous gastric surgery
- ◊ Pernicious anemia, adenomatous polyps, gastric ulcer
- ◊ Chronic atrophic gastritis
- ◊ Radiation exposure
- ◊ History of alcohol use/smoking

Oesophageal Cancer:

- ◊ Genetic causes - tylosis (hyperkeratosis palmaris et plantaris)
- ◊ History of alcohol use/smoking
- ◊ History of chronic or acute inflammation (e.g. GERD, Barrett's esophagus, caustic ingestion), achalasia (esophageal motility disorder)
- ◊ Human papilloma virus
- ◊ Sclerotherapy
- ◊ Plummer-Vinson syndrome (dysphagia, associated with iron deficiency anemia)

Liver cancer:

- ◊ History of cirrhosis (including alcoholic, biliary cirrhosis), other chronic liver dysfunction
- ◊ History of alcohol use/smoking
- ◊ Hepatitis B, C
- ◊ Hemochromatosis
- ◊ Indigestion of food contaminated with fungal aflatoxins (in subtropical regions)

Pancreatic Cancer:

- ◊ History of alcohol use/smoking
- ◊ Obesity
- ◊ Diet (red meat)
- ◊ History of chronic pancreatitis or long-standing diabetes mellitus (primarily in women).
- ◊ Inherited predisposition (hereditary pancreatitis, familial adenomatous polyposis, etc.)

Renal Cancer (renal cell carcinoma):

- ◊ Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting
- ◊ Obesity
- ◊ Hypertension
- ◊ Phenacetin-containing analgesics taken in large amounts

- History of renal transplantation
- Exposure to radiopaque dyes, asbestos, cadmium, and leather tanning and petroleum products
- Inherited von Hippel-Lindau disease (VHL) disease, Adult polycystic kidney disease, Tuberous sclerosis

Bladder Cancer:

- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting
- Industrial exposure to aromatic amines in dyes, paints, solvents, leather dust, inks, combustion products, rubber, and textiles
- Occupation - painting, driving trucks, and working with metal
- Prior spinal cord injuries with long-term indwelling catheters

Prostate Cancer:

- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting
- History of high-grade prostatic intraepithelial neoplasia (PIN)
- Genome changes-deletion of chromosome 3 and fusion of TMPRSS2 and ERG genes
- Testosterone level
- History of sexually transmitted diseases
- History of vasectomy
- History of exposure to cadmium
- History of genitor-urinary infections

Head and Neck Cancer:

- History of alcohol use/smoking
- Exposure to Human papilloma virus (HPV) or Epstein-Barr virus (EBV)
- History of poor oral hygiene and/or poor nutrition
- Exposure to asbestos, wood dust, paint fumes or chemicals
- History of Gastroesophageal reflux disease (GERD) or laryngopharyngeal reflux disease (LPRD)

Brain tumors (gliomas and meningiomas):

- Exposure to radiation
- Exposure to vinyl chloride, Pesticides
- Immune system disorders
- Hormone replacement therapy

Larynx Cancer:

- History of alcohol use/smoking
- Asbestos exposure
- Any activity requiring loud speech, exposure to sudden and frequent temperature changes
- Frequent hoarseness, frequent and persistent cough
- Persistently swollen neck glands
- Tonsillectomy and laryngeal surgery

Nasal and Paranasal Sinus Cancer:

- Woodworking, any dust/flour chronic exposure
- History of Infection with human papillomavirus (HPV)
- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting

Mouth and Oropharyngeal Cancer:

- ◊ History of alcohol use/smoking
- ◊ History of poor oral hygiene
- ◊ Chronic mucosal/gum irritation / ill-fitting dentures
- ◊ Betel-Nut Chewing (Indian populations)
- ◊ History of syphilis or viral infections
- ◊ Impaired immunity – AIDS, transplant with anti-rejection drugs
- ◊ Precancerous mouth plaques – Leukoplakia or erythroplasia
- ◊ History of cancer of the aero-digestive tract

Melanoma, basal cell carcinoma, squamous cell carcinoma of skin:

- ◊ History of prolonged sun exposure (UV radiation) – severe blistering sunburns, frequent tanning, use of sunlamps and tanning booths
- ◊ History of living close to equator or at high elevation
- ◊ History of skin conditions – Dysplastic nevus, Xeroderma pigmentosum, nevoid basal cell carcinoma syndromes
- ◊ Skin type – fair (pale) skin – burns easily, freckles
- ◊ Eye color – blue, green or gray, Hair color – blond or red
- ◊ Use of medication causing sensitivity to sun – antibiotics, hormones, antidepressants,
- ◊ Immune system depression – AIDS, leukemias, etc.
- ◊ Exposure to arsenic, coal tar or creosote
- ◊ For eye localization- history of oculodermal melanocytosis or Dysplastic nevus syndrome

_____

Health Practitioner Name (Print)

_____

Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

Bristol Myers Squibb™
P.O BOX 4000, B.3140
Princeton, NJ-08543-4000

[Case_ ID]

Adverse Event Report Questionnaire
TL Hepatobiliary disorders (hepatitis_hepatic failure_hepatotoxicity) (Thalidomide)

INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:

Patient Demographics:

Patient's date of birth (DD-MMM-YYYY): _____ Gender: ☐Male ☐ Female
Age: _____.

Race/Ethnicity: _____ ☐ Aboriginal ☐African American ☐ Asian
☐ American Indian or Alaskan Native ☐ Native Hawaiian or other Pacific Islander
☐ Torres Strait Islander ☐ White ☐ Black ☐ Non Hispanic

Age Group:_____

Note: Please provide Age Group if Patient's Date of Birth or Age is not available.

Age Group Definition: Neonate: 0 - 27 days, Infant: 28 days to 23 months, Child: 2 years to 11years, Adolescent: 12 years to 18 years, Adult: More than 18 years and less than or equal to 65 years and Elderly: equal or greater than 66 years)

Suspect Products: Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

	Suspect Product #1	Suspect Product #2	Suspect Product #3
Product name			
Daily dose and regimen			
Route of administration			
Indication			
Start date or treatment duration (DD-MMM-YYYY)			
Stop date (DD-MMM-YYYY)			
Lot/Batch number(s)			
Expiration date(s)			
Action Taken with the suspect product			

(Choose from one of the following for action Taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown)

Adverse Event (AE) Description: Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

	Adverse Event #1	Adverse Event #2	Adverse Event #3	Adverse Event #4

Add Diagnosis Here →				
Start Date (DD/MMM/YYYY)				
Stop Date (DD/MMM/YYYY)				
Time lag if AE occurred after cessation of treatment with the suspect product(s):				
Required Hospitalization (Yes/No)				
Life-Threatening (Yes/No)				
Persistent or significant disability (Yes/No)				
Congenital abnormality (Yes/No)				
Cause of Death (Yes/No)				
Treatment of Adverse Event				
Outcome (recovery and sequelae, if any)				
Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No)				
Did the event recur after reintroducing (Yes/No)				

Please summarize course of reported events including signs and symptoms in chronological order:

_____

_____

_____

Diagnostic tests (use additional pages if needed)**:** Please indicate test unit where applicable.

Date	Test Name	Pre-treatment value	AE onset value	AE resolution value	Normal low	Normal high

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

_____

_____

Concomitant Medications (use additional pages if needed)**:**

Did the Patient take any concomitant medication? ☐ Yes (please complete below) ☐ No ☐ Unknown

Medication Name	Daily dose and regimen	Route of administration	Indication	Start date DD-MMM-YYYY	Stop date DD-MMM-YYYY

Other Etiological Factors: ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical and/or drug history (please specify), including start date or duration:

_____

_____

_____

☐ Family history (please specify): _____
☐ Drug/alcohol/tobacco abuse: _____
☐ Other (please specify): _____

Additional questions:

Did the patient have a history of liver disease, hepatitis, alcohol or substance abuse? Please include the onset dates of disease.

Did the patient have any of the following pre-existing diseases: cardiac disease, congestive heart failure, or infections?

What clinical signs and symptoms (with dates) were observed? Jaundice, bleeding, encephalopathy?

Did the patient receive other chemotherapies simultaneously with Thalidomide?
☐ Yes ☐ No
If yes, please provide drug name, dosing and therapy dates.

Drug name	Dose	Start date	End date

Did the patient receive other chemotherapies prior to taking Thalidomide?

☐ Yes ☐ No

If yes, please provide drug name, dosing and therapy dates.

Drug name	Dose	Start date	End date

Was there any concurrent use of potentially hepatotoxic drugs or products?
☐ Yes ☐ No
If yes, please provide drug name, dosing and therapy dates.

Drug name	Dose	Start date	End date

Please provide the treatment/intervention received due to the event.

Please provide the results of the following diagnostics: (include dates completed)

Liver biopsy:

CT scans:

MRI:

Ultrasound:

Health Practitioner Name (Print)

Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

Bristol Myers Squibb™
P.O BOX 4000, B.3140
Princeton, NJ-08543-4000

Adverse Event Report Questionnaire

Infections/ Opportunistic infections

INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:

Patient Demographics:

Patient's date of birth (DD/MMM/YYYY) or age: _____. Gender: ☐ Male
Ethnicity: _____ ☐ Female

Age Group:_____

(Age Group Definition: Neonate=0.002 years-0.077 years, Infant=0.078 years-1.999 years,Child=2 years-11.999 years, Adolescent=12 years-17.999 years, Adult=18 years-64.999 years and Elderly=65 years-199 years)

Suspect Products: Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

	Suspect Product #1	Suspect Product #2	Suspect Product #3
Product name			
Daily dose and regimen			
Route of administration			
Indication			
Start date or treatment duration (DD/MMM/YYYY)			
Stop date (DD/MMM/YYYY)			
Lot/Batch number(s)			
Expiration date(s)			

Adverse Event (AE) Description: Please provide list diagnosis vs symptoms/signs if diagnosis is available.

	Adverse Event #1	Adverse Event #2	Adverse Event #3	Adverse Event #4
Add Diagnosis Here →				
Start Date (DD/MMM/YYYY)				
Stop Date (DD/MMM/YYYY)				
Time lag if AE occurred after cessation of treatment with the suspect product(s):				
Required Hospitalization (yes/no)				
Cause of Death (Y/N)				
Treatment of Adverse Event				
Outcome (recovery and sequelae, if any)				

Please list signs and symptoms in chronological orderr (e.g. localized/generalized redness, heat, fever, swelling, itching, burning, pus or discharge, nausea and vomiting):

_____

Site of infection:

☐Bone ☐Cardiovascular ☐Gastrointestinal ☐Skin
☐Hepatobiliary ☐Kidney ☐Upper Respiratory ☐HEENT
☐Blood ☐CNS ☐Lower Respiratory ☐Other, specify: _____
☐Joint ☐Prostate ☐Genitourinary

Diagnostic tests (use additional pages if needed)**:** Please indicate test unit where applicable.

Test Name	Location	AE onset value	AE resolution value	Normal low	Normal high
Biopsy					
Cultures (specify):					
Radiographic studies (speficy):					
CSF analysis					
Staining					
PCR					
Cytology					

Were there any complications caused by the infection? If yes, please provide details.

Please specify causative agent (please mark with an "X"):

☐Pneumocystis jirovecii ☐JC polyomavirus ☐Cryptosporidium
☐Candida albicans ☐Acinetobacter baumanni ☐Herpes virus
☐Staphylococcus aureus ☐Toxoplasma gondii ☐Mycobacterium
☐Streptococcus pyogenes ☐Cytomegalovirus ☐Other, specify: _____
☐Pseudomonas aeruginosa ☐Aspergillus species

Did the adverse event(s) abate after suspect product(s) was stopped or dose reduced (if applicable)? ☐ Yes ☐ No
Did the adverse event(s) re-appear after re-introduction of the suspect product(s) (if applicable)? ☐ Yes ☐ No

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

Concomitant Medications (use additional pages if needed)**:**

Did the Patient take any concomitant medication? ☐ Yes (please complete below) ☐ No ☐ Unknown

Please mark with an "x" all that apply, and specify medication details below:

☐Corticosteroids ☐Immunosuppressant therapy ☐Biologics ☐Other, specify: _____
☐Chemotherapy ☐Interferon

Medication Name	Daily dose and regimen	Route of administration	Indication	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)

Other Etiological Factors: ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical and/or drug history (please specify), including start date or duration:

_____

_____

_____

☐Skin laceration or penetration
☐Animal/insect/human bite (please specify): _____
☐Recent hospitalization (provide details): _____
☐Malignancy (please specify): _____
☐Organ transplantation (please specify): _____
☐HIV-infection/ AIDS
☐Autoimmune disorder (please specify): _____
☐Pregnancy
☐Advanced age
☐Vaccination history (please specify): _____
☐Malnutrition Other (please specify): _____
☐Family history (please specify): _____
☐Drug/alcohol/tobacco abuse: _____
☐Other (please specify): _____

Additional questions:

_____
Health Practitioner Name (Print)

_____
Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

7 page(s) excluding cover page

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

The MAH shall agree the details of a controlled access programme with the National Competent Authorities and must implement such programme nationally to ensure that:

- Prior to launch, all doctors who intend to prescribe Thalidomide BMS and all pharmacists who may dispense Thalidomide BMS receive a Direct Healthcare Professional Communication as described below.
- Prior to prescribing (where appropriate, and in agreement with the National Competent Authority, dispensing) all healthcare professionals who intend to prescribe (and dispense) Thalidomide BMS are provided with an Educational Healthcare Professional's Kit containing the following:
  - Educational Healthcare Professional brochure
  - Educational brochures for patients
  - Patient card
  - Risk awareness forms
  - Information on where to find latest Summary of Product Characteristics (SmPC)
- The MAH shall implement a pregnancy prevention programme (PPP) in each Member State. Details of the PPP should be agreed with the National Competent Authorities in each Member State and put in place prior to the launch of the medicinal product.
- The MAH should agree the final text of the Direct Healthcare Professional Communication and the contents of the Educational Healthcare Professional's Kit with the National Competent Authority in each Member State prior to launch of the medicinal product and ensure that the materials contain the key elements as described below.
- The MAH should agree on the implementation of the controlled access programme in each Member State.
- Prior to approval by the National Competent Authority and prior to launch of the medicinal product, the MAH should ensure that the educational materials are provided to and reviewed by the national patients' organisations or if such an organisation does not exist or can not be involved, by a relevant patients group. Patients involved should be preferably naïve to the history of thalidomide. Results of the user testing will have to be provided to the National Competent Authority and final materials validated at a national level.
- The MAH should also agree with each Member State prior to launch of the medicinal product:
  - The most appropriate strategies to monitor the off-label use within national territories
  - The collection of detailed data to understand demographics of target population, indication and number of women of child bearing potential in order to monitor the off-label use within national territory.
- The MAH shall notify the EMA and the appropriate national patients and victims representatives of the proposed launch date before launch in each Member State.

Key elements to be included

Direct Healthcare Professional Communication (prior to launch)

The Direct Healthcare Professional Communication shall consist of two parts:

- A core text as agreed by the CHMP
- National specific requirements agreed with the National Competent Authority regarding:
  - Distribution of the medicinal product
  - Procedures to ensure that all appropriate measures have been performed prior to Thalidomide BMS being dispensed

Educational Healthcare Professional's Kit

The Educational Healthcare Professional's Kit shall contain the following elements:

Educational Healthcare Professional brochure

- History and background of thalidomide
- Maximum duration of treatment prescribed
  - 4 weeks for women with childbearing potential
  - 12 weeks for men and women without childbearing potential
- Teratogenicity and the need to avoid foetal exposure
- Guidance on handling the blister or capsule of Thalidomide BMS for healthcare professionals and caregivers
- Obligations of the healthcare professionals who intend to prescribe or dispense Thalidomide BMS
  - Need to provide comprehensive advice and counselling to patients
  - That patients should be capable of complying with the requirements for the safe use of Thalidomide BMS
  - Need to provide patients with the appropriate patient educational brochure, patient card and/or equivalent tool
- Safety advice relevant to all patients
  - Description and management of ischaemic heart disease (including myocardial infarction)
  - Local country specific arrangements for a prescription for thalidomide to be dispensed
  - That any unused capsules should be returned to the pharmacist at the end of the treatment
  - That the patient should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Thalidomide BMS
- Description of the PPP and categorisation of patients based on sex and childbearing potential
  - Algorithm for implementation of PPP

  - Definition of women of childbearing potential (WCBP) and actions the prescriber should take if unsure
- Safety advice for women of childbearing potential
  - The need to avoid foetal exposure
  - Description of the PPP
  - Need for effective contraception (even if the woman has amenorrhoea) and definition of effective contraception
  - That if she needs to change or stop using her method of contraception she should inform:
    - The physician prescribing her contraception that she is on thalidmoide
    - The physician prescribing thalidomide that she has stopped or changed her method of contraception
  - Pregnancy test regime
    - Advice on suitable tests
    - Before commencing treatment
    - During treatment based on method of contraception
    - After finishing treatment
  - Need to stop Thalidomide BMS immediately upon suspicion of pregnancy
  - Need to tell treating doctor immediately upon suspicion of pregnancy
- Safety advice for men
  - The need to avoid foetal exposure
  - The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraception (even if the man has had a vasectomy)
    - During Thalidomide BMS treatment
    - For at least 7 days following final dose
  - That he should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Thalidomide BMS treatment
  - That if his partner becomes pregnant whilst he is taking Thalidomide BMS or shortly after he has stopped taking Thalidomide BMS he should inform his treating doctor immediately
- Requirements in the event of pregnancy
  - Instructions to stop Thalidomide BMS immediately upon suspicion of pregnancy, if female patient
  - Need to refer patient to physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
  - Local contact details for reporting of any suspected pregnancy immediately
- Local contact details for reporting adverse reactions

Educational Brochures for patients

The Educational brochures for patients should be of 3 types:

- Brochure for women of childbearing potential and their partner
- Brochure for women patients who are not of childbearing potential
- Brochure for male patients

All educational brochures for patients should contain the following elements:

- That thalidomide is teratogenic
- That thalidomide may cause ischemic heart disease, (including myocardial infarction)
- Description of the patient card and its necessity
- Guidance on handling Thalidomide BMS for patients, caregivers and family members
- National or other applicable specific arrangements for a prescription for Thalidomide BMS to be dispensed
- That the patient must not give Thalidomide BMS to any other person
- That the patient should not donate blood during treatment (including during dose interruptions) and for at least 7 days after discontinuation of Thalidomide BMS treatment
- That the patient should tell their doctor about any adverse events
- That any unused capsules should be returned to the pharmacist at the end of the treatment

The following information should also be provided in the appropriate brochure:

Brochure for women patients with childbearing potential

- The need to avoid foetal exposure
- Description of the PPP
- The need for effective contraception and definition of effective contraception
- That if she needs to change or stop using her method of contraception she should inform:
  - The physician prescribing her contraception that she is on thalidomide
  - The physician prescribing thalidomide that she has stopped or changed her method of contraception
- Pregnancy test regime
  - Before commencing treatment
  - During treatment (including dose interruptions), at least every 4 weeks except in case of confirmed tubal sterilisation
  - After finishing treatment
- The need to stop Thalidomide BMS immediately upon suspicion of pregnancy
- The need to contact their doctor immediately upon suspicion of pregnancy

Brochure for male patients

- The need to avoid foetal exposure
- The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraception (even if the man has had vasectomy)
  - During Thalidomide BMS treatment (including dose interruptions)
  - For at least 7 days following final dose
- That if his partner becomes pregnant he should inform his treating doctor immediately
- That he should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Thalidomide BMS treatment

Patient Card or equivalent tool

The patient card shall contain the following elements:

- Verification that appropriate counselling has taken place
- Documentation of childbearing potential status
- Check box (or similar) which physician ticks to confirm that patient is using effective contraception (if woman of childbearing potential)
- Pregnancy test dates and results

Risk Awareness Forms

There should be 3 types of risk awareness forms:

- Women of childbearing potential
- Women of non-childbearing potential
- Male patient

All risk awareness forms should contain the following elements:

- Teratogenicity warning
- Patients receive the appropriate counselling prior to treatment initiation
- Affirmation of patient understanding of the risk of thalidomide and the PPP measures
- Date of counselling
- Patient details, signature and date
- Prescriber name, signature and date
- Aim of this document i.e., as stated in the PPP: "The aim of the risk awareness form is to protect patients and any possible foetuses by ensuring that patients are fully informed of and understand the risk of teratogenicity and other adverse reactions associated with the use of thalidomide. It is not a contract and does not absolve anybody from his/her

responsibilities with regard to the safe use of the product and prevention of foetal exposure."

Risk awareness forms for women of childbearing potential should also include:

- Confirmation that the physician has discussed the following:
  - The need to avoid foetal exposure
  - That if she is pregnant or plans to be, she must not take thalidomide
  - That she understands the need to avoid thalidomide use during pregnancy and to apply effective contraceptive measures without interruption, at least 4 weeks before starting treatment, throughout the entire duration of treatment, and at least 4 weeks after the end of treatment
  - That if she needs to change or stop using her method of contraception she should inform:
    - The physician prescribing her contraception that she is taking Thalidomide BMS
    - The physician prescribing Thalidomide BMS that she has stopped or changed her method of contraception
  - Of the need for pregnancy tests i.e. before treatment, at least every 4 weeks during treatment and after treatment
  - Of the need to stop Thalidomide BMS immediately upon suspicion of pregnancy
  - Of the need to contact their doctor immediately upon suspicion of pregnancy
  - That she should not share the medicinal product with any other person
  - That she should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Thalidomide BMS
  - That she should return the unused capsules to the pharmacist at the end of treatment

Risk awareness forms for women with no childbearing potential should also include:

- Confirmation that the physician has discussed the following:
  - That she should not share the medicinal product with any other person
  - That she should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Thalidomide BMS
  - That she should return the unused capsules to the pharmacist at the end of treatment

Risk awareness forms for male patients should also include:

- Confirmation that the physician has discussed the following:
  - The need to avoid foetal exposure
  - That thalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a WCBP not on effective contraception (even if the man has had vasectomy)

- That if his partner becomes pregnant he should inform his treating doctor immediately and always use a condom
- That he should not share the medicinal product with any other person
- That he should not donate blood or semen during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Thalidomide BMS
- That he should return the unused capsules to the pharmacist at the end of treatment