PART VI - SUMMARY OF THE RISK MANAGEMENT PLAN

1. SUMMARY OF RISK MANAGEMENT PLAN FOR THALIDOMIDE CELGENE (THALIDOMIDE)

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

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

This summary of the RMP for Thalidomide Celgene 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 Celgene's RMP.

1.1. The Medicine and what it is Used for

Thalidomide Celgene 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 Celgene's benefits can be found in Thalidomide Celgene'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.

1.2. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Thalidomide Celgene, together with measures to minimise such risks and the proposed studies for learning more about Thalidomide Celgene'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 Celgene, 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.

1.3. List of Important Risks and Missing Information

Important risks of Thalidomide Celgene 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 Celgene. 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 Table 1.

Table 1: List of Important Risks and Missing Information

Important Identified Risks:	• Teratogenicity • Severe infections (sepsis, septic shock and viral reactivation of hepatitis B) • Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)
Important Potential Risks:	• Ischaemic heart disease (including myocardial infarction) • Other second primary malignancies (SPM) • Hepatic disorders (hepatocellular and cholestatic liver injury) • Off-label use
Missing Information:	• None

1.4. Summary of Important Risks

Table 2: Important Identified Risk: Teratogenicity

Important Identified Risk: 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.

Table 2: Important Identified Risk: Teratogenicity (Continued)

Important Identified Risk: Teratogenicity	
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 Celgene 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:** • Celgene PPP o Educational programme • Direct HCP communication prior to launch • Educational material for HCPs and patients • HCP booklets, patient assessment algorithm, patient treatment initiation forms, patient card or equivalent tools. • Patient booklets o 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. o Advice provided by SmPC, outlined in direct HCP communication and detailed in Educational materials.
Additional Pharmacovigilance Activities	Additional monitoring of implementation of Thalidomide Celgene PPP on a country specific basis in accordance with local legal framework and with the agreement of the relevant National Competent Authority (NCA): To monitor the implementation of the Celgene PPP on a country specific basis. Patient materials comprehension validation: To monitor the implementation of the Celgene 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.

Table 3: 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)	
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 (Freifeld, 2008). 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 (Miceli, 2006). 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 (Yeo, 2004; Roche, 2011).
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.

Table 4: Important Identified Risk: Acute Myeloid Leukaemia and Myelodysplastic Syndromes

Important Identified Risk: 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 (2006) 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 (Travis, 2006). 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% (Altekruse, 2010). • **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 (Travis, 2006). One of the best-characterised and most potent leukemogenic alkylating drugs is melphalan (US Department of Health and Human Services, 2011). • **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 (Pedersen-Bjergaard, 2005). Therapy-associated AML or MDS are well-recognised complications of therapy in MM patients. Significant transformation risk extends for many years following therapy.

Table 4: Important Identified Risk: Acute Myeloid Leukaemia and Myelodysplastic Syndromes (Continued)

Important Identified Risk: Acute Myeloid Leukaemia and Myelodysplastic Syndromes	
Risk Factors and Risk Groups (Continued)	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 (Dierickx, 2011). 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 (Dierickx, 2011). 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 (Bensinger, 2009). 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 (Weinstock, 2006). • **Granulocyte Colony-stimulating Factor Therapy** Recent guidelines for cancer care support the use of G-CSF prophylaxis in specific therapeutic circumstances (Renwick, 2009). Despite the usefulness of G-CSF therapy, increased risks of AML or MDS associated with G-CSF use have been described. Lyman (2010) 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 (Lynch, 2008; Varkonyi, 2001).

Table 4: Important Identified Risk: Acute Myeloid Leukaemia and Myelodysplastic Syndromes (Continued)

Important Identified Risk: Acute Myeloid Leukaemia and Myelodysplastic Syndromes	
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.
Additional Pharmacovigilance Activities	Long-term follow-up and solicited reporting for AML and MDS in clinical trials. Letter to investigator-sponsors of ongoing Celgene non-sponsored clinical trials informing of the need for long-term follow-up for AML and MDS and to report any cases to Celgene as serious adverse events (SAEs).

Table 5: Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction)

Important Potential Risk: 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 (Tahir, 2008). Additional known risk factors include hypercholesterolemia and sedentary lifestyle (Wilson, 1998). 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 (Grethlein, 2009).

Table 5: Important Potential Risk: Ischaemic Heart Disease (Including Myocardial Infarction) (Continued)

Important Potential Risk: Ischaemic Heart Disease (Including Myocardial 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

Table 6: Important Potential Risk: Other Second Primary Malignancies

Important Potential Risk: 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 (2006) 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, 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 (Travis, 2006). 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% (Altekruse, 2010). • **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,

Table 6: Important Potential Risk: Other Second Primary Malignancies (Continued)

Important Potential Risk: Other Second Primary Malignancies	
Risk Factors and Risk Groups (Continued)	lomustine, mechlorethamine, melphalan, prednimustine, and semustine (Travis, 2006). One of the best-characterised and most potent leukemogenic alkylating drugs is melphalan (US Department of Health and Human Services, 2011). • **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 (Pedersen-Bjergaard, 2005). 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 (Dierickx, 2011). 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 (Dierickx, 2011). 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 (Bensinger, 2009). 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 (Weinstock, 2006). • **Granulocyte Colony-stimulating Factor Therapy** Recent guidelines for cancer care support the use of G-CSF prophylaxis in specific therapeutic circumstances (Renwick, 2009). Despite the usefulness of G-CSF therapy, increased risks of AML or MDS associated with G-CSF use have been described. Lyman (2010) 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 (Lynch, 2008; Varkonyi, 2001).

Table 6: Important Potential Risk: Other Second Primary Malignancies (Continued)

Important Potential Risk: Other Second Primary Malignancies	
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. Letter to investigator-sponsors of ongoing Celgene non-sponsored clinical trials informing of the need for long-term follow-up for other SPM and to report any cases to Celgene as SAEs. Invasive SPM will be considered important medical events

Table 7: Important Potential Risk: Hepatic Disorders (Hepatocellular and Cholestatic Liver Injury)

Important Potential Risk: 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 (Floyd, 2006; Rodriguez-Frias, 2007). 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 (Loriot, 2008). 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 (Kyle, 1975) and between 1985 to 1998 (Kyle, 2003), Kyle and colleagues noted that a palpable liver was present in 21% and 4% of patients at the time of initial diagnosis, respectively.

Table 7: Important Potential Risk: Hepatic Disorders (Hepatocellular and Cholestatic Liver Injury) (Continued)

Important Potential Risk: Hepatic Disorders (Hepatocellular and Cholestatic Liver Injury)	
Risk Factors and Risk Groups (Continued)	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 (Talamo, 2006). 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 (Thomas, 1973). 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.

Table 8: Important Potential Risk: Off-label Use

Important Potential Risk: 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.
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.

1.5. Postauthorisation Development Plan

1.5.1. Studies which are Conditions of the Marketing Authorisation

None.

1.5.2. Other Studies or Activities in the Postauthorisation Development Plan

Additional monitoring of implementation of Thalidomide Celgene 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 Celgene PPP on a country specific basis.

Patient materials comprehension validation

Purpose of activity: To monitor the implementation of the Celgene 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.

Letter to investigator-sponsors of ongoing Celgene non-sponsored clinical trials informing of the need for long-term follow-up for SPM and to report any cases to Celgene as SAEs

Purpose of activity: Long-term safety evaluation and monitoring of SPM in the context of clinical trials. Invasive SPM will be considered important medical events.

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