Summary of the risk management plan

Summary of risk management plan for Lenalidomide Mylan (lenalidomide)

This is a summary of the risk management plan (RMP) for Lenalidomide Mylan. The RMP details important risks of lenalidomide, how these risks can be minimised, and how more information will be obtained about lenalidomide's risks and uncertainties (missing information).

Lenalidomide Mylan's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how it should be used.

This summary of the RMP for Lenalidomide Mylan should be read in the context of all the 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 Lenalidomide Mylan's RMP.

I. The medicine and what it is used for

Lenalidomide Mylan as monotherapy is authorised for maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.

Lenalidomide Mylan as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone (see SmPC section 4.2) is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

Lenalidomide Mylan in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

It contains lenalidomide as the active substance and it is given by oral route.

Further information about the evaluation of Lenalidomide Mylan’s benefits can be found in lenalidomide Mylan’s EPAR, including in its plain-language summary, available on the EMA website.

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

Important risks of Lenalidomide Mylan, together with measures to minimise such risks and the proposed studies for learning more about Lenalidomide Mylan'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 package leaflet and SmPC addressed to patients and healthcare professionals;
- 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 public (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, via signal management activities and PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

In the case of Lenalidomide Mylan, these routine measures are supplemented with additional risk minimisation measures, mentioned under relevant risks below.

II.A List of important risks and missing information

Important risks of Lenalidomide Mylan are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken by patients. 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 Lenalidomide Mylan. 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 (e.g. on the long-term use of the medicine/use in special patient populations etc.);

Table 1 Summary of safety concerns

List of important risks and missing information	
Important identified risks	• Teratogenicity • Serious infection due to neutropenia • Second primary malignancies (SPM) Important Identified Risk Related to Indication/Target Population:

List of important risks and missing information	
	• For FL (follicular lymphoma): TFR
Important potential risks	• Cardiac failure • Cardiac arrhythmias • Ischaemic heart disease (including myocardial infarction) • Off-label use
Missing information	None

II.B Summary of important risks

Important Identified Risk: Teratogenicity	
Evidence for linking the risk to the medicine	Lenalidomide is structurally related to thalidomide, which is known to cause serious birth defects and death of the foetus. In nonclinical studies, lenalidomide induced malformations similar to those described with thalidomide. Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy.
Risk factors and risk groups	The 'at risk' group comprises females of child bearing potential or female partners of male patients treated with lenalidomide and there are no risk factors
Risk minimisation measures	Routine risk minimisation measures • Section 4.3 of SmPC: Contraindicated in pregnant women and in females of child bearing potential unless all the conditions of the pregnancy prevention programme are met. • Section 4.4 of SmPC: Warnings and Precautions for use a. Criteria for women of non-child bearing potential b. Counselling c. Contraception d. Pregnancy testing e. Precautions for men

Important Identified Risk: Teratogenicity	
	f. Additional precautions g. Reference to educational materials, prescribing and dispensing restrictions. • Section 4.6 of SmPC: Fertility, pregnancy and lactation. • Sections 4.8 and 5.3 of SmPC: The potential teratogenic effects of lenalidomide are highlighted. • Pack size: The pack is based on a maximum 4-week supply of capsules to ensure that females of child bearing potential are required to obtain a new monthly prescription with a medically supervised pregnancy test. • Legal status: Lenalidomide is subject to restricted medical prescription. **Additional risk minimisation measures** • Pregnancy prevention programme (PPP) • HCP and patient educational materials • Patient card to document childbearing status, counselling and pregnancy testing. 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 product. The MAH shall agree the details of a controlled distribution system with the National Competent Authorities and must implement such programme nationally to ensure that: prior to prescribing (and where appropriate, and in agreement with the national competent authority, prior to dispensing) all healthcare professionals who intend to prescribe (and dispense) Lenalidomide Mylan are provided with a physician information pack containing: • the educational health care professional's kit

Important Identified Risk: Teratogenicity	
	• educational brochures for patients, • Patient cards and Summary of product characteristics (SmPC) and package leaflet and labelling.

Important identified Risk: Serious Infection due to Neutropenia	
Evidence for linking the risk to the medicine	In clinical trials conducted for the originator product, neutropenia has been reported as a consequence of lenalidomide treatment; ≥ Grade 3 and ≥ Grade 4 infections have occurred in the context of neutropenia (any grade).
Risk factors and risk groups	Haematological malignancies by themselves or by virtue of their therapeutic strategies, chemotherapy, radiation or haematopoietic stem cell transplant put patients at risk of infections. Risk factors include myeloma-related innate immunodeficiency, which involves various arms of the immune system and includes B-cell dysfunction, polyclonal hypogammaglobulinemia, treatment associated organ dysfunctions and comorbidities including renal failure, respiratory compromise, severe alimentary mucosal damage, dexamethasone induced hyperglycemia, multisystem involvement due to myeloma associated deposition diseases. Elderly age is also risk factor. Lenalidomide treatment in combination with dexamethasone in MM patients with at least one prior therapy is associated with a higher incidence of neutropenia compared to placebo-dexamethasone treated patients.
Risk minimisation measures	Routine risk minimisation measures • section 4.2 of SmPC: Dose reduction advice for neutropenia. • section 4.4 of SmPC: Warning of neutropenia, and infection with or without neutropenia and advice for monitoring patients, including blood testing for neutropenia. Advice regarding establishing HBV status before treatment, use in

Important identified Risk: Serious Infection due to Neutropenia	
	patients previously infected with HBV and monitoring for signs and symptoms of active HBV infection throughout therapy. • Listed as ADR in section 4.8 of SmPC. • Advice to patients in PL, including that the doctor is advised to check if the patient has ever had hepatitis B infection prior to starting lenalidomide treatment. Additional risk minimisation measures • Not applicable as there are no additional risk minimisation measures for this safety concern

Important identified Risk: Second Primary Malignancy	
Evidence for linking the risk to the medicine	In clinical trials, AML and B-cell malignancies have been reported in patients treated with lenalidomide. Based on clinical trial data, lenalidomide may increase the risk of NMSC. Patients with multiple myeloma also have an increased risk of NMSC. Patients treated with lenalidomide may be at increased risk of developing new cancers. The reason is not clear, but further investigations are being undertaken for the originator product.
Risk factors and risk groups	An increase of second primary malignancies (SPM) has been observed in clinical trials in previously treated myeloma patients receiving lenalidomide/dexamethasone (3.98 per 100 person-years) compared to controls (1.38 per 100 person-years). Non-invasive SPM comprise basal cell or squamous cell skin cancers. Most of the invasive SPMs were solid tumour malignancies. In clinical trials of newly diagnosed multiple myeloma patients not eligible for transplant, a 4.9-fold increase in incidence rate of hematologic SPM (cases of AML, MDS) has been observed in patients receiving lenalidomide in combination with melphalan and

Important identified Risk: Second Primary Malignancy	
	prednisone until progression (1.75 per 100 person-years) compared with melphalan in combination with prednisone (0.36 per 100 person-years). A 2.12-fold increase in incidence rate of solid tumour SPM has been observed in patients receiving lenalidomide (9 cycles) in combination with melphalan and prednisone (1.57 per 100 person-years) compared with melphalan in combination with prednisone (0.74 per 100 person-years). In patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months, the hematologic SPM incidence rate (0.16 per 100 person-years) was not increased as compared to thalidomide in combination with melphalan and prednisone (0.79 per 100 person-years). A 1.3-fold increase in incidence rate of solid tumour SPM has been observed in patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months (1.58 per 100person years) compared to thalidomide in combination with melphalan and prednisone (1.19 per 100 person-years). In newly diagnosed multiple myeloma patients receiving lenalidomide in combination with bortezomib and dexamethasone, the hematologic SPM incidence rate was 0.00 – 0.16 per 100 person-years and the incidence rate of solid tumour SPM 0.21 – 1.04 per 100 person-years. The increased risk of secondary primary malignancies associated with lenalidomide is relevant also in the context of NDMM after stem cell transplantation. Though this risk is not yet fully characterized, it should be kept in mind when considering and using Lenalidomide Mylan in this setting. The incidence rate of hematologic malignancies, most notably AML, MDS and B-cell malignancies (including Hodgkin's

Important identified Risk: Second Primary Malignancy	
	lymphoma), was 1.31 per 100 person-years for the lenalidomide arms and 0.58 per 100 person-years for the placebo arms (1.02 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT). The incidence rate of solid tumour SPMs was 1.36 per 100 person-years for the lenalidomide arms and 1.05 per 100 person years for the placebo arms (1.26 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT). The risk of occurrence of hematologic SPM must be taken into account before initiating treatment with lenalidomide either in combination with melphalan or immediately following high-dose melphalan and ASCT. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.
Risk minimisation measures	Routine risk minimisation measures • Section 4.4 of SmPC mentioning warning of second primary malignancy and advice for cancer screening. • Listed as ADRs in section 4.8 of SmPC. • Advice to patients provided in product label Additional risk minimisation measures • HCP and patient educational material (HCP and patient brochure)

Important Identified Risk Related to Indication/Target Population: For FL (follicular lymphoma): TFR	
Evidence for linking the risk to the medicine	Based on clinical trial data, lenalidomide may increase the risk of TFR in patients with CLL and other lymphomas.

Important Identified Risk Related to Indication/Target Population: For FL (follicular lymphoma): TFR	
Risk factors and risk groups	Tumour flare reaction has been associated with greater tumour burden in patients with CLL.
Risk minimisation measures	Routine risk minimisation measures • Section 4.2 and 4.4 of SmPC • Listed as an ADR in Section 4.8 of SmPC. Additional risk minimisation measures • HCP educational material (HCP brochure)

Important Potential Risk: Cardiac Failure	
Evidence for linking the risk to the medicine	Based on clinical trial data, a higher incidence of cardiac failure has been observed; the reason for this is not clear.
Risk factors and risk groups	No particular risk groups or risk factors have been identified for lenalidomide. In MM no differences in frequency, severity, serious outcomes and apparent risk level of cardiac failure AEs have been observed. General risk factors for congestive heart failure include increasing age, previous heart disease, diabetes, hypertension, amyloidosis and previous anthracycline based chemotherapy treatment.
Risk minimisation measures	Routine risk minimisation measures • Listed as ADRs in section 4.8 of SmPC. Additional risk minimisation measures • Not applicable as there are no additional risk minimisation measures for this safety concern

Important Potential Risk: Cardiac Arrhythmias	
Evidence for linking the risk to the medicine	Based on clinical trial data, a higher incidence of cardiac arrhythmia has been observed in lenalidomide arm

Important Potential Risk: Cardiac Arrhythmias	
Risk factors and risk groups	No particular risk groups or risk factors have been identified for lenalidomide. Standard risk factors for atrial fibrillation include advancing age, European ancestry, body size (greater height and body mass index), electrocardiography features (left ventricular hypertrophy, left atrial enlargement), diabetes, systolic blood pressure and presence of cardiovascular disease (i.e., CHD, Heart failure, valvular heart disease). Other factors include clinical and subclinical hyperthyroidism, chronic kidney disease and heavy alcohol consumption. The association of atrial fibrillation was independent of indication for use. Risks were increased in patients with asthma or chronic obstructive pulmonary disease, but also in patients with rheumatic, allergic or malignant haematologic diseases.
Risk minimisation measures	Routine risk minimisation measures • Listed as ADRs in section 4.8 of SmPC. • Listed in PL. Additional risk minimisation measures • Not applicable as there are no additional risk minimisation measures for this safety concern

Important Potential Risk: Ischaemic Heart disease (including Myocardial Infarction)	
Evidence for linking the risk to the medicine	In clinical trials, ischaemic heart disease has been reported in patients treated with lenalidomide. Myocardial infarction occurs relatively often in individuals of the older age groups that most often develop the target indication of MM.
Risk factors and risk groups	Risk factors for 10-year coronary risk based upon the Framingham Heart Study include elevated blood pressure, elevated cholesterol, high-density lipoprotein c, presence of diabetes and cigarette

Important Potential Risk: Ischaemic Heart disease (including Myocardial Infarction)	
	smoking. These factors are in addition to well-known relationships between coronary risk and age and gender. In Europe, smoking remains a major public health issue and about 20% of death from CVD in men and about 3% of deaths from CVD in women are due to smoking. Levels of obesity are high across Europe in both adults and children and participation in physical activity is low. The prevalence of diabetes in Europe is high and has increased rapidly over the last ten years, increasing by more than 50% in many countries.
Risk minimisation measures	Routine risk minimisation measures • The association between ischaemic heart disease and lenalidomide is unknown. • Myocardial infarction is included in sections 4.4 and 4.8 of the SmPC. Additional risk minimisation measures • Not applicable as there are no additional risk minimisation measures for this safety concern

Important Potential Risk: Off-label Use	
Evidence for linking the risk to the medicine	There is potential for the use of lenalidomide in indications other than the approved indications.
Risk factors and risk groups	Not applicable
Risk minimisation measures	Routine risk minimisation measures • Collection of off-label use data detailed in section 4.4 of SmPC. Additional risk minimisation measures • Not applicable as there are no additional risk minimisation measures for this safety concern

II.C Post-authorisation development plan

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

In line with the requirements set out for the innovator product, the Applicant shall assess effectiveness and compliance with the PPP and shall agree with each Member State prior to marketing the set-up of national measures.

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Pregnancy Prevention Programme (Category 3)	Monitoring of implementation and effectiveness of the PPP	Teratogenicity	Routine PSURs in line with EURD list	In line with DLP of the latest EURD list

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

There are no studies required for Lenalidomide Mylan.