Part VI: Summary of the risk management plan

Summary of risk management plan for thalidomide

This is a summary of the risk management plan (RMP) for Thalidomide 50 mg capsules. The RMP details important risks of Thalidomide 50 mg capsules, how these risks can be minimised, and how more information will be obtained about Thalidomide's risks and uncertainties (missing information).

Thalidomide summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Thalidomide 50 mg capsules should be used.

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

I. The medicine and what it is used for

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

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

Important risks of Thalidomide 50 mg capsules, together with measures to minimise such risks and the proposed studies for learning more about Thalidomide'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 patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Thalidomide 50 mg capsules, 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 50 mg capsules are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 50 mg capsules. 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);

Important identified and potential risks, together with missing information, are summarised in Table:

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

II.B Summary of important risks

Important Identified Risk: Teratogenicity	
Risk minimisation measures	**Routine risk minimisation measures:** **<u>SmPC</u>** Section 4.3 states that thalidomide is contraindicated in pregnant women and in females of childbearing potential (FCBP) unless all the conditions of the 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 states that where teratogenicity is listed as an adverse drug reaction (ADR). **<u>PL</u>** The Package Leaflet (PL) warns of the potential teratogenic effects of thalidomide and the need to avoid pregnancy. *Pack size: None* **Additional risk minimisation measures:** **Pregnancy Prevention Programme (PPP)** o *Educational programme* ▪ *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 (WCBP), effective contraceptive measures for women of childbearing potential, regular pregnancy testing for women of childbearing potential. o Advice provided by SmPC, and detailed in Educational materials.
Additional Pharmacovigilance Activities	Additional monitoring of implementation of PPP on a country specific basis in accordance with local legal framework and with agreement of the relevant NCA

Important Identified Risk: Severe infections (sepsis, septic shock and viral reactivation of hepatitis B)	
Risk minimisation measures	**Routine risk minimisation measures:** **<u>SmPC</u>** Section 4.4 and 4.8 of SmPC states that, where advise is given to the patients regarding monitoring of severe

Important Identified Risk: Severe infections (sepsis, septic shock and viral reactivation of hepatitis B)	
	infections <u>Section 4.8 states that where severe infections are listed as ADRs.</u> **<u>PL</u>** Section 2 and 4 of the 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. Pack size: None **Additional risk minimisation measures** None

Important Identified Risk: Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)	
Risk minimisation measures	**Routine risk minimisation measures:** **<u>SmPC</u>** 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 states that AML/MDS are listed as ADRs. **<u>PL</u>** Advice to patients in PL regarding the possibility of developing AML and MDS. Pack size: None **Additional risk minimisation measures** None

Important Potential Risk: Ischaemic heart disease (including myocardial infarction)	
Risk minimisation measures	**Routine risk minimisation measures:** **<u>SmPC</u>** Section 4.2 which provides advice regarding Thromboprophylaxis for ischaemic heart disease Section 4.4 which warns of the risk factors for Myocardial Infarction (MI). Section 4.8 which lists myocardial infarction as an ADR. **<u>PL</u>**

Important Potential Risk: Ischaemic heart disease (including myocardial infarction)	
	Advice to patients in PL regarding the risk of ischaemic heart disease. Pack size: None **Additional risk minimisation measures** Educational material for healthcare professionals (HCPs) and patients

Important Potential Risk: Other second primary malignancies (SPM)	
Risk minimisation measures	**Routine risk minimisation measures:** **SmPC** Section 4.4 warns that other Second Primary Malignancies (SPM), such as Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS) have been observed after thalidomide treatment. **PL** Advice to patients in PL regarding the risk of Second Primary Malignancies **(**SPM). Pack size: None **Additional risk minimisation measures** None

Important Potential Risk: Hepatic disorders (hepatocellular and cholestatic liver injury)	
Risk minimisation measures	**Routine risk minimisation measures:** **SmPC** Section 4.4 where doctors are advised to monitor patients for liver function, particularly in case of pre-existing liver disorder or concomitant use of medicinal product susceptible to induce liver dysfunction. Section 4.8 where hepatic disorders are listed as ADRs. **PL** Advice to patients in PL regarding the risk of hepatic disorders. Pack size: None **Additional risk minimisation measures** None proposed

Important Potential Risk: Off-label use	
Risk minimisation measures	**Routine risk minimisation measures:** The SmPC details the risks associated with thalidomide use and actions to be taken in the event of specific AEs. **Recommendations from PL:** No specific measures for prevention are known. Pack size: None **Additional risk minimisation measures:** Educational material for healthcare professionals (HCPs) and patients 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.

Missing information: None

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Thalidomide 50 mg capsules.

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

S. No	**Study short name**	**Purpose of the study**
1.	Pregnancy Prevention Programme (PPP) of Thalidomide	Minimisation of the risk of teratogenicity and to provide education on the risk and the necessary steps to prevent foetal exposure
2.	Monitoring of off-label use of Thalidomide 50 mg hard capsules	To monitor off-label use