Summary of risk management plan for Lenalidomide Krka d.d.

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

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

This summary of the RMP for Lenalidomide Krka d.d. 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 Lenalidomide Krka d.d.'s RMP.

I. The medicine and what it is used for

Lenalidomide Krka d.d. is authorised for treatment of multiple myeloma, myleodysplactic syndromes and follicular lymphoma (see SmPC for the full indication). It contains lenalidomide as the active substance and it is given orally.

Further information about the evaluation of Lenalidomide Krka d.d.'s benefits can be found in Lenalidomide Krka d.d.'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/lenalidomide-krka-dd.

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

Important risks of Lenalidomide Krka d.d. , together with measures to minimise such risks and the proposed studies for learning more about Lenalidomide Krka d.d. '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 Lenalidomide Krka d.d., 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 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 Lenalidomide Krka d.d. 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 Lenalidomide Krka d.d. . 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);

List of important risks and missing information	
Important identified risks	Teratogenicity
	Serious Infection due to Neutropenia
	Secondary primary malignancies
	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

The safety information in the proposed Product Information is aligned to the reference medicinal product.

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 minimisation measures	Routine risk minimisation measures
	Section 4.3 of SmPC: contraindicated in pregnant women and in FCBP unless all the conditions of the Celgene PPP are met.
	Section 4.4 of SmPC: warnings and precautions for use
	- Criteria for women of non-childbearing potential
	- Counselling
	- Contraception
	- Pregnancy testing
	- Precautions for men
	- Additional precautions
	- 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 FCBP 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:
	- Lenalidomide Pregnancy Prevention Programme
	- Educational programme for healthcare professionals and patients:
	  ○ HCP kit,
	  ○ Treatment algorithm, pregnancy reporting form, patient card, patient guide and checklists

Important identified risk: Teratogenicity	

	- Therapy management
	  o Criteria for determining FCBP, Contraceptive measures and pregnancy testing for FCBP
	  o Advice in SmPC and educational materials
	- System to ensure appropriate measures have been completed
	- Patient card to document childbearing status, counselling and pregnancy testing.

Additional pharmacovigilance activities	Monitoring of Pregnancy Prevention Programme implementation See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Serious infection due to Neutropenia	
Evidence for linking the risk to the medicine	In clinical trials, neutropenia has been reported as a consequence of lenalidomide treatment; ≥ Grade 4 and ≥ Grade 3 infections have occurred in the context of neutropenia (any grade).
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 that patients should report febrile episodes promptly. Advice regarding establishing HBV status before treatment, use in patients previously infected with HBV and monitoring for signs and symptoms of active HBV infection throughout therapy. - Listed as ADRs 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 None

Important identified risk: Secondary primary malignancies	
Evidence for linking the risk to the	In clinical trials, AML and B-cell malignancies have been

medicine	reported in patients treated with lenalidomide. Based on clinical trial data, lenalidomide may increase the risk of NMSC. Patients with MM also have an increased risk of NMSC. Patients treated with lenalidomide may be at increased risk of developing new cancers. The reason for this is not clear, but further investigations are being undertaken.
Risk minimisation measures	Routine risk minimisation measures - Section 4.4 of SmPC warning of SPM and advice for cancer screening. - Listed as ADRs in Section 4.8 of SmPC. - Advice to patients provided in PL. Additional risk minimisation measures Educational information for healthcare professionals

For FL indication: **Important identified risk: 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.
Risk minimisation measures	Routine risk minimisation measures - Section 4.2 of SmPC advice on dose interruption - Section 4.4 of SmPC warning - Listed as ADRs in Section 4.8 of SmPC. Additional risk minimisation measures Educational information for healthcare professionals

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 minimisation measures	Routine risk minimisation measures - Listed as ADRs in Section 4.8 of SmPC. - Listed in PL. Additional risk minimisation measures

Important potential risk: Cardiac failure	
	None

Important potential risk: Cardiac arrhythmias	
Evidence for linking the risk to the medicine	Based on clinical trial data, a higher incidence of cardiac arrhythmia was observed in the lenalidomide arm.
Risk minimisation measures	Routine risk minimisation measures - Listed as ADRs in Section 4.8 of SmPC. - Listed in PL. Additional risk minimisation measures None

Important potential risk: Ischemic heart disease (including Myocardial Infarction)	
Evidence for linking the risk to the medicine	In clinical trials, IHD 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 indications of MM, MDS and FL.
Risk minimisation measures	Routine risk minimisation measures - Myocardial infarction is included in Sections 4.4 and 4.8 of the SmPC. Additional risk minimisation measures None

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 minimisation measures	Routine risk minimisation measures - Collection of off-label use data detailed in Section 4.4 of SmPC.

Important potential risk: Off-label use	
	Additional risk minimisation measures 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 Lenalidomide Krka d.d.

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

Monitoring of Pregnancy Prevention Programme implementation

Purpose of the study: Monitoring of implementation and the effectiveness of PPP