EU Risk Management Plan for Lenalidomide Krka (procedure EMEA/H/C/005348)

RMP version to be assessed as part of this application:

RMP Version number: 2.0
Data lock point for this RMP: 28.10.2025
Date of final sign off: 28.10.2025

Rationale for submitting an updated RMP: A request received during the renewal procedure (EMA/R/0000272358 to update the RMP in accordance with the changes to the reference product's RMP within 6 months after the completion of the reference product variation Revlimid (EMEA/H/C/000717/II/130), which also includes the RMP modifications (BMS, Revlimid, version 42.2) published on EMA (EPAR).

Summary of significant changes in this RMP:

- Update of Part II Module SVII to update information regarding the published innovator's RMP (Revlimid, version 42.2., published 9/9/2025)
- Update of Part II Module SVIII and Part VI to delete Important identified risk *For MCL (mantle cell lymphoma) or FL (follicular lymphoma): Tumour flare reaction (TFR)* and to reclassify Important potential risks *Cardiac failure, Cardiac arrhythmias* and *Ischaemic heart disease (including myocardial infarction)* from Important potential risks to Important identified risks
- Update of Part III to delete Specific adverse reaction follow-up questionnaire for Tumour flare reaction (TFR)
- Update of Part V to delete Important identified risk *For MCL (mantle cell lymphoma) or FL (follicular lymphoma): Tumour flare reaction (TFR)*
- Update of Part VI to delete Important identified risk *For MCL (mantle cell lymphoma) or FL (follicular lymphoma): Tumour flare reaction (TFR)* and to reclassify Important potential risks *Cardiac failure, Cardiac arrhythmias* and *Ischaemic heart disease (including myocardial infarction)* as Important identified risks
- Update of Annex 4 to delete Specific adverse reaction follow-up questionnaire for Tumour flare reaction (TFR)
- Update of Annex 6 to delete information regarding Tumour flare reaction (TFR) and progression to AML in MDS patients in Educational Healthcare Professional brochure
- Update of Annex 8
- Administrative changes

Other RMP versions under evaluation: None

Details of the currently approved RMP:

Version number: 1.1

Approved with procedure: EMEA/H/C/005348

Date of approval (opinion date): 02/07/2024

QPPV name: Irena Orel MD, MSc

QPPV signature:

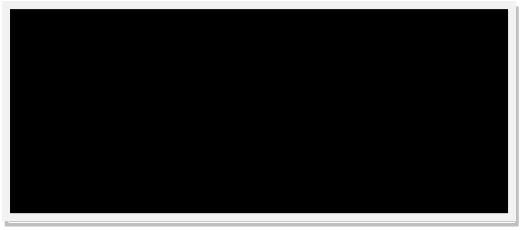

Table of content

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	lenalidomide
Pharmacotherapeutic group(s) (ATC Code)	Other immunosuppressants L04AX04
Marketing Authorisation Holder or Applicant	KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia and Krka's subsidiaries
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Lenalidomide Krka
Marketing authorisation procedure	centralised
Brief description of the product	Chemical class: thalidomide analog
	Summary of mode of action: Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1). In haematopoietic cells, lenalidomide binding to cereblon recruits substrate proteins Aiolos and Ikaros, lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation resulting in direct cytotoxic and immunomodulatory effects. Specifically, lenalidomide inhibits proliferation and enhances apoptosis of certain haematopoietic tumour cells (including MM plasma tumour cells, follicular lymphoma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK, T and NK T cells. In MDS Del (5q), lenalidomide selectively inhibits the abnormal clone by increasing the apoptosis of Del (5q) cells. The combination of lenalidomide and rituximab increases ADCC and direct tumor apoptosis in follicular lymphoma cells.

	The lenalidomide mechanism of action also includes additional activities such as anti-angiogenic and proerythropoietic properties. Lenalidomide inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes.
	Important information about its composition: NA
Hyperlink to the Product Information	Please refer to module 1.3.1 of dossier
Indication(s) in the EEA	Current (if applicable): <u>Multiple myeloma</u> Lenalidomide Krka as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation. Lenalidomide Krka as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant. Lenalidomide Krka in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy. <u>Myelodysplastic syndromes</u> Lenalidomide Krka as monotherapy is indicated for the treatment of adult patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. <u>Mantle cell lymphoma</u> Lenalidomide Krka as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma. <u>Follicular lymphoma</u>

<table>
<tr><td></td><td>Lenalidomide Krka in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3a).</td></tr>
<tr><td></td><td>Proposed (if applicable):
Not applicable</td></tr>
<tr><td>Dosage in the EEA</td><td>Current (if applicable):
Lenalidomide treatment should be supervised by a physician experienced in the use of anti-cancer therapies.

For all indications described below:
• Dose is modified based upon clinical and laboratory findings.
• Dose adjustments, during treatment and restart of treatment, are recommended to manage Grade 3 or 4 thrombocytopenia, neutropenia, or other Grade 3 or 4 toxicity judged to be related to lenalidomide.
• In case of neutropenia, the use of growth factors in patient management should be considered.
• If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

<u>Posology</u>

<u>Newly diagnosed multiple myeloma (NDMM)</u>

Lenalidomide in combination with dexamethasone until disease progression in patients who are not eligible for transplant
Lenalidomide treatment must not be started if the Absolute Neutrophil count (ANC) is < 1.0 x 10^9/L, and/or platelet counts are < 50 x 10^9/L.

Recommended dose
The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1 to 21 of repeated 28-day cycles.
The recommended dose of dexamethasone is 40 mg orally once daily on days 1, 8, 15 and 22 of repeated 28-day cycles. Patients may continue lenalidomide and dexamethasone therapy until disease progression or intolerance.

Dose reduction steps
<table><tr><td></td><td>Lenalidomide[a]</td><td>Dexamethasone[a]</td></tr><tr><td>Starting dose</td><td>25 mg</td><td>40 mg</td></tr><tr><td>Dose level -1</td><td>20 mg</td><td>20 mg</td></tr></table></td></tr>
</table>

Dose level -2	15 mg	12 mg
Dose level -3	10 mg	8 mg
Dose level- 4	5 mg	4 mg
Dose level -5	2.5 mg	Not applicable

[a] Dose reduction for both products can be managed independently

Thrombocytopenia

When platelets	Recommended course
Fall to < 25 x 10^9/L	Stop lenalidomide dosing for remainder of cycle[a]
Return to ≥ 50 x 10^9/L	Decrease by one dose level when dosing resumed at next cycle

[a] If Dose limiting toxicity (DLT) occurs on > day15 of a cycle, lenalidomide dosing will be interrupted for at least the remainder of the current 28-day cycle.

Absolute Neutrophil count (ANC) - *neutropenia*

When ANC	Recommended course[a]
First falls to < 0.5 x 10^9/L Returns to ≥ 1 x 10^9/L when neutropenia is the only observed toxicity	Interrupt lenalidomide treatment Resume lenalidomide at starting dose once daily
Returns to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at dose level -1 once daily
For each subsequent drop below < 0.5 x 10^9/L Returns to ≥ 0.5 x 10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level once daily.

[a] At the physician's discretion, if neutropenia is the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of lenalidomide.

For hematologic toxicity the dose of lenalidomide may be re-introduced to the next higher dose level (up to the starting dose) upon improvement in bone marrow function (no hematologic toxicity for at least 2 consecutive cycles: ANC ≥1.5 x 10^9/L with a platelet count ≥ 100 x 10^9/L at the beginning of a new cycle).

<u>Lenalidomide in combination with bortezomib and dexamethasone followed by lenalidomide and dexamethasone until disease progression in patients</u>

who are not eligible for transplant

Initial treatment: Lenalidomide in combination with bortezomib and dexamethasone

Lenalidomide in combination with bortezomib and dexamethasone must not be started if the ANC is < 1.0 x 10^9/L, and/or platelet counts are < 50 x 10^9/L.

The recommended starting dose is lenalidomide 25 mg orally once daily days 1-14 of each 21-day cycle in combination with bortezomib and dexamethasone. Bortezomib should be administered via subcutaneous injection (1.3 mg/m^2 body surface area) twice weekly on days 1, 4, 8 and 11 of each 21-day. For additional information on the dose, schedule and dose adjustments of medicinal products administered with lenalidomide, see Section 5.1 and the corresponding Summary of Product Characteristics.

Up to eight 21-day treatment cycles (24 weeks of initial treatment) are recommended.

Continued treatment: Lenalidomide in combination with dexamethasone until progression

Continue lenalidomide 25 mg orally once daily on days 1-21 of repeated 28-day cycles in combination with dexamethasone. Treatment should be continued until disease progression or unacceptable toxicity.

Dose reduction steps

	Lenalidomide[a]
Starting dose	25 mg
Dose level -1	20 mg
Dose level -2	15 mg
Dose level -3	10 mg
Dose level- 4	5 mg
Dose level -5	2.5 mg

[a] Dose reduction for all products can be managed independently

Thrombocytopenia

When platelets	Recommended course
Fall to < 30 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 50 x 10^9/L	Resume lenalidomide at dose level -1 once daily
For each subsequent drop below 30 x 10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose

Return to ≥ 50 x 10^9/L	level once daily

Absolute Neutrophil count (ANC) - neutropenia

When ANC	Recommended course[a]
First falls to < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Returns to ≥ 1 x 10^9/L when neutropenia is the only observed toxicity	Resume lenalidomide at starting dose once daily
Returns to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at dose level -1 once daily
For each subsequent drop below < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Returns to ≥ 0.5 x 10^9/L	Resume lenalidomide at next lower dose level once daily.

[a] At the physician's discretion, if neutropenia is the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of lenalidomide.

<u>Lenalidomide in combination with melphalan and prednisone followed by lenalidomide maintenance in patients who are not eligible for transplant</u>

Lenalidomide treatment must not be started if the ANC is < 1.5 x 10^9/L, and/or platelet counts are < 75 x 10^9/L.

Recommended dose

The recommended starting dose is lenalidomide 10 mg orally once daily on days 1 to 21 of repeated 28-day cycles for up to 9 cycles, melphalan 0.18 mg/kg orally on days 1 to 4 of repeated 28-day cycles, prednisone 2 mg/kg orally on days 1 to 4 of repeated 28-day cycles. Patients who complete 9 cycles or who are unable to complete the combination therapy due to intolerance are treated with lenalidomide monotherapy as follows: 10 mg orally once daily on days 1 to 21 of repeated 28-day cycles given until disease progression.

Dose reduction steps

	Lenalidomide	Melphalan	Prednisone
Starting dose	10 mg[a]	0.18 mg/kg	2 mg/kg
Dose level -1	7.5 mg	0.14 mg/kg	1 mg/kg
Dose level -2	5 mg	0.10 mg/kg	0.5 mg/kg
Dose level -3	2.5 mg	Not applicable	0.25 mg/kg

[a] If neutropenia is the only toxicity at any dose level, add granulocyte

colony stimulating factor (G-CSF) and maintain the dose level of lenalidomide

Thrombocytopenia

When platelets	Recommended course
First fall to < 25 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 25 x 10^9/L	Resume lenalidomide and melphalan at dose level -1
For each subsequent drop below 30 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L	Resume lenalidomide at next lower dose level (dose level -2 or -3) once daily.

Absolute Neutrophil count (ANC) - neutropenia

When ANC	Recommended course[a]
First falls to < 0.5 x 10^9/L[a]	Interrupt lenalidomide treatment
Returns to ≥ 0.5 x 10^9/L when neutropenia is the only observed toxicity	Resume lenalidomide at starting dose once daily
Returns to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at dose level -1 once daily
For each subsequent drop below < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Returns to ≥ 0.5 x 10^9/L	Resume lenalidomide at next lower dose level once daily.

[a] At the physician's discretion, if neutropenia is the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of lenalidomide.

<u>Lenalidomide maintenance in patients who have undergone autologous stem cell transplantation (ASCT)</u>

Lenalidomide maintenance should be initiated after adequate haematologic recovery following ASCT in patients without evidence of progression.

Lenalidomide must not be started if the ANC is < 1.0 x 10^9/L, and/or platelet counts are < 75 x 10^9/L.

Recommended dose

The recommended starting dose is lenalidomide 10 mg orally once daily continuously (on days 1 to 28 of repeated 28-day cycles) given until

disease progression or intolerance. After 3 cycles of lenalidomide maintenance, the dose can be increased to 15 mg orally once daily if tolerated.

Dose reduction steps

	Starting dose (10 mg)	If dose increased (15 mg)[a]
Dose level -1	5 mg	10 mg
Dose level -2	5 mg (days 1-21 every 28 days)	5 mg
Dose level -3	Not applicable	5 mg (days 1-21 every 28 days)
	Do not dose below 5 mg (days 1-21 every 28 days)	

Thrombocytopenia

When platelets	Recommended course
Fall to < 30 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L	Resume lenalidomide at dose level -1 once daily
For each subsequent drop below 30 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L	Resume lenalidomide at next lower dose level once daily

Absolute Neutrophil count (ANC) - neutropenia

When ANC	Recommended course[a]
Falls to < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Returns to ≥ 0.5 x 10^9/L	Resume lenalidomide at dose level -1 once daily
For each subsequent drop below < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Returns to ≥ 0.5 x 10^9/L	Resume lenalidomide at next lower dose level once daily

[a] At the physician's discretion, if neutropenia is the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of lenalidomide.

<u>*Multiple myeloma with at least one prior therapy*</u>

Lenalidomide treatment must not be started if the ANC < 1.0 x 10^9/L, and/or platelet counts < 75 x 10^9/L or, dependent on bone marrow infiltration by plasma cells, platelet counts < 30 x 10^9/L.

Recommended dose

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1 to 21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily on days 1 to 4 every 28 days.

Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

Dose reduction steps

Starting dose	25 mg
Dose level -1	15 mg
Dose level -2	10 mg
Dose level -3	5 mg

Thrombocytopenia

When platelets	Recommended course
First fall to < 30 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L	Resume lenalidomide at dose level -1
For each subsequent drop below 30 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L	Resume lenalidomide at next lower dose level (dose level -2 or -3) once daily. Do not dose below 5 mg once daily.

Absolute Neutrophil count (ANC) - neutropenia

When ANC	Recommended course[a]
First falls to < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Returns to ≥ 0.5 x 10^9/L when neutropenia is the only observed toxicity	Resume lenalidomide at starting dose once daily
Returns to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at dose level -1 once daily
For each subsequent drop below < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Returns to ≥ 0.5 x 10^9/L	Resume lenalidomide at next lower

	dose level (dose level -1, -2 or -3) once daily. Do not dose below 5 mg once daily.

[a] At the physician's discretion, if neutropenia is the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of lenalidomide.

Myelodysplastic syndromes (MDS)

Lenalidomide treatment must not be started if the ANC < 0.5 x 10^9/L and/or platelet counts < 25 x 10^9/L.

Recommended dose

The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1 to 21 of repeated 28-day cycles.

Dose reduction steps

Starting dose	10 mg once daily on days 1 to 21 every 28 days
Dose level -1	5 mg once daily on days 1 to 28 every 28 days
Dose level -2	2.5 mg once daily on days 1 to 28 every 28 days
Dose level -3	2.5 mg every other day 1 to 28 every 28 days

Thrombocytopenia

When platelets	Recommended course
Fall to < 25 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 25 x 10^9/L - < 50 x 10^9/L on at least 2 occasions for ≥ 7 days or when the platelet count recovers to ≥ 50 x 10^9/L at any time	Resume lenalidomide at next lower dose level (dose level -1, -2 or -3)

Absolute neutrophil count (ANC) - neutropenia

When ANC	Recommended course
Falls to < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Returns to ≥ 0.5 x 10^9/L	Resume lenalidomide at next lower dose level (dose level -1, -2 or -3)

Discontinuation of lenalidomide

Patients without at least a minor erythroid response within 4 months of

therapy initiation, demonstrated by at least a 50% reduction in transfusion requirements or, if not transfused, a 1g/dl rise in haemoglobin, should discontinue lenalidomide treatment.

Mantle cell lymphoma (MCL)

Recommended dose

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1 to 21 of repeated 28-day cycles.

Dose reduction steps

Starting dose	25 mg once daily on days 1 to 21, every 28 days
Dose Level -1	20 mg once daily on days 1 to 21, every 28 days
Dose Level -2	15 mg once daily on days 1 to 21, every 28 days
Dose Level -3	10 mg once daily on days 1 to 21, every 28 days
Dose Level -4	5 mg once daily on days 1 to 21, every 28 days
Dose Level -5	2.5 mg once daily on days 1 to 21, every 28 days[1] 5 mg every other day on days 1 to 21, every 28 days

[1] - In countries where the 2.5 mg capsule is available.

Thrombocytopenia

When platelets	Recommended course
Fall to < 50 x 10^9/L Return to ≥ 60 x 10^9/L	Interrupt lenalidomide treatment and conduct Complete Blood Count (CBC) at least every 7 days Resume lenalidomide at next lower level (dose level -1)
For each subsequent drop below 50 x 10^9/L Return to ≥60 x 10^9/L	Interrupt lenalidomide treatment and conduct the CBC at least every 7 days Resume lenalidomide at next lower level (dose level -2, -3, -4 or -5). Do not dose below dose level -5

Absolute neutrophil count (ANC) - neutropenia

When ANC	Recommended course
Falls to < 1 x 10^9/L for at least 7 days or Falls to < 1 x 10^9/L with associated fever (body temperature ≥ 38.5°C) or	Interrupt lenalidomide treatment and conduct the CBC at least every 7 days

Falls to < 0.5 x 10^9/L	
Returns to ≥ 1 x 10^9/L	Resume lenalidomide at next lower dose level (dose level -1)
For each subsequent drop below 1 x 10^9/L for at least 7 days or drop to < 1 x 10^9/L with associated fever (body temperature ≥ 38.5°C) or drop to < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Returns to ≥1 x 10^9/L	Resume Lenalidomide at next lower dose level (dose level -2, -3, -4, -5). Do not dose below dose level -5

Follicular lymphoma (FL)

Lenalidomide treatment must not be started if the ANC is < 1 x 10^9 /L, and/or platelet count < 50 x 10^9/L, unless secondary to lymphoma infiltration of bone marrow.

Recommended dose

The recommended starting dose of lenalidomide is 20 mg, orally once daily on days 1 to 21 of repeated 28- day cycles for up to 12 cycles of treatment. The recommended starting dose of rituximab is 375 mg/m^2 intravenously (IV) every week in Cycle 1 (days 1, 8, 15, and 22) and day 1 of every 28-day cycle for cycles 2 through 5.

Dose reduction steps

Starting dose	20 mg once daily on days 1-21, every 28 days
Dose Level -1	15 mg once daily on days 1-21, every 28 days
Dose Level -2	10 mg once daily on days 1-21, every 28 days
Dose Level -3	5 mg once daily on days 1-21, every 28 days

For dose adjustments due to toxicity with rituximab, refer to the corresponding summary of product characteristics.

Thrombocytopenia

When platelets	Recommended course
Fall to < 50 x 10^9/L	Interrupt lenalidomide treatment and conduct CBC at least every 7 days
Return to ≥ 50 x 10^9/L	Resume at next lower dose level (dose level -1)

For each subsequent drop below 50 x 10^9/L Return to ≥50 x 10^9/L	Interrupt lenalidomide treatment and conduct CBC at least every 7 days Resume lenalidomide at next lower dose level (dose level -2, -3). Do not dose below dose level -3.

Absolute neutrophil count (ANC) - neutropenia

When ANC	Recommended course[a]
Falls to < 1.0 x 10^9/L for at least 7 days or Falls to < 1.0 x 10^9/L with associated fever (body temperature ≥ 38.5°C) or Falls to < 0.5 x 10^9/L	Interrupt lenalidomide treatment and conduct CBC at least every 7 days
Returns to ≥ 1.0 x 10^9/L	Resume lenalidomide at next lower dose level (dose level -1)
For each subsequent drop below 1.0 x 10^9/L for at least 7 days or drop to < 1.0 x 10^9/L with associated fever (body temperature ≥ 38.5°C) or drop to < 0.5 x 10^9/L	Interrupt lenalidomide treatment and conduct CBC at least every 7 days
Returns to ≥1.0 x 10^9/L	Resume lenalidomide at next lower dose level (dose level -2, -3). Do not dose below dose level -3

[a] At the physician's discretion, if neutropenia is the only toxicity at any dose level, add G-CSF

<u>*Mantle cell lymphoma (MCL) or follicular lymphoma (FL)*</u>

Tumour lysis syndrome (TLS)

All patients should receive TLS prophylaxis (allopurinol, rasburicase or equivalent as per institutional guidelines) and be well hydrated (orally) during the first week of the first cycle or for a longer period if clinically indicated. To monitor for TLS, patients should have a chemistry panel drawn weekly during the first cycle and as clinically indicated. Lenalidomide may be continued (maintain dose) in patients with laboratory TLS or Grade 1 clinical TLS, or at the physician's discretion, reduce dose by one level and continue lenalidomide. Vigorous intravenous hydration should be provided and appropriate medical management according to the local standard of care, until correction of electrolyte abnormalities. Rasburicase therapy may be needed to

	reduce hyperuricaemia. Hospitalisation of the patient will be at physician's discretion. In patients with Grade 2 to 4 clinical TLS, interrupt lenalidomide and obtain a chemistry panel weekly or as clinically indicated. Vigorous intravenous hydration should be provided and appropriate medical management according to the local standard of care, until correction of electrolyte abnormalities. Rasburicase therapy and hospitalisation will be at physician's discretion. When the TLS resolves to Grade 0, restart lenalidomide at next lower dose per physician's discretion (see section 4.4). *Tumour flare reaction* At the physician's discretion, lenalidomide may be continued in patients with Grade 1 or 2 tumour flare reaction (TFR) without interruption or modification. At the physician's discretion, therapy with non-steroidal anti-inflammatory drugs (NSAIDs), limited duration corticosteroids, and/or narcotic analgesics may be administered. In patients with Grade 3 or 4 TFR, withhold treatment with lenalidomide and initiate therapy with NSAIDs, corticosteroids and/or narcotic analgesics. When TFR resolves to ≤ Grade 1, restart lenalidomide treatment at the same dose level for the rest of the cycle. Patients may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR (see section 4.4). *<u>All indications</u>* For other Grade 3 or 4 toxicities judged to be related to lenalidomide, treatment should be stopped and only restarted at next lower dose level when toxicity has resolved to ≤ Grade 2 depending on the physician's discretion. Lenalidomide interruption or discontinuation should be considered for Grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, anaphylactic reaction, Grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected and should not be resumed following discontinuation from these reactions.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): 2.5 mg hard capsules 5 mg hard capsules 7.5 mg hard capsules

	10 mg hard capsules 15 mg hard capsules 20 mg hard capsules 25 mg hard capsules
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable.

Part II: Module SII - Non-clinical part of the safety specification

Not applicable.

Part II: Module SIII - Clinical trial exposure

Not applicable.

Part II: Module SIV - Populations not studied in clinical trials

Not applicable.

Part II: Module SV - Post-authorisation experience

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Not applicable.

Part II: Module SVII - Identified and potential risks

Not applicable. The list of safety concerns is obtained from innovator's RMP (MAH Bristol-Myers Squibb Pharma EEIG, version 42.2, sign off date 20.05.2025) published on EMA's site: https://www.ema.europa.eu/en/medicines/human/EPAR/revlimid (Last updated: 09/09/2025).

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Teratogenicity
	Serious Infection due to Neutropenia
	Second primary malignancies (SPM)
	Cardiac failure
	Cardiac arrhythmias
	Ischaemic heart disease (including myocardial infarction)
Important potential risks	Off-label use
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

III.1.1 Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection

- **Specific follow-up questionnaires:**

Specific adverse reaction follow-up questionnaires for the following safety concerns:	**Follow-up Form Title**
Teratogenicity	Pregnancy follow up forms: • Pregnancy Background (Patient or Partner of Patient) • Pregnancy Follow-up (Patient or Partner of Patient) • Pregnancy Outcome (Patient or Partner of Patient) • Infant Follow-up
Serious Infection due to Neutropenia	Neutropenia
Second Primary Malignancies (SPM)	Second Primary Malignancies
Cardiac failure	Cardiac failure
Cardiac arrhythmias	Cardiac arrhythmia and ECG Changes
Ischaemic heart disease (including myocardial infarction)	Myocardial infarction

Please see Annex 4 for Specific adverse reaction follow-up questionnaires.

III.1.2 Other forms of routine pharmacovigilance activities

- **Expedited Reporting and Follow-up of Pregnancy**
    - The pregnancy capture and follow-up procedure are detailed below. 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 lenalidomide treatment. Like thalidomide and lenalidomide, lenalidomide is an immunomodulatory agent with expected teratogenic effects in humans. The PPP reflects advice, guidance and direction obtained from the Member States during the implementation process. The same principles on obtaining follow-up data on pregnancies are implemented in all territories where lenalidomide is 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 lenalidomide.
  - To obtain information on all reported pregnancies of female partners of male patients exposed to lenalidomide.
  - To determine the root cause of all pregnancies and hence failures of the PPP.
- The capture of reports of pregnancy is enhanced by the Educational Materials in the Educational HCP's Kit which make reference to the requirement to report all suspected pregnancies to the local 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 pregnancy. Similar advice is also provided with reference to female partners of male patients.
- Database of Pregnancy Reports: All reports of pregnancies received are entered into Global Safety Database. This includes all Consumer reports in addition to HCP reports. Any abnormal pregnancy test result (eg, β-hCG elevated and positive urine pregnancy test) is immediately processed. EU 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 representative 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 deputy. All reports of abnormal pregnancy test results are followed up with the prescriber and follow-up information sent to Health Authorities.
- Frequency/Duration of Follow-up: Upon receipt of a notification of pregnancy, the pregnancy specific follow-up questionnaire is sent to the reporter. Upon receipt of this information by MAH, dates for further follow-up actions are tracked. The HCP/Obstetrician is also sent 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.
- 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 are reported on an expedited basis within 15 days.

- **<u>Analysis of Adverse Drug Reactions of Special Interest within the required PSURs:</u>**
  - 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.
  - In addition, data regarding pregnancy exposure to lenalidomide are targeted for review and specifically discussed in the PSUR document. These data include all pregnancy case reports collected during the specified period together with cumulative data. Non-medically confirmed case reports of suspected foetal exposure are also provided, whenever applicable. Non-patient exposure in pregnant females (eg, a nurse opening

the capsules, laboratory technician, or carer) is also provided with the corresponding outcome in each PSUR.

III.2 Additional pharmacovigilance activities

Monitoring of Pregnancy Prevention Programme (PPP) implementation

Study short name and title: Monitoring of Pregnancy Prevention Programme implementation

Rationale and study objectives: Monitoring of implementation and the effectiveness of PPP

Study design: The monitoring of the implementation and effectiveness of the PPP (category 3 study) will be agreed on a country-specific basis with the relevant National Competent Authority (NCA) in accordance with local legal framework. Methods are anticipated to be similar to the activities in place for the reference medicinal product. Moreover, data will be collected on a regular basis after product launch and the results will be reported in PSURs, in accordance with the PSUR schedule.

Study population: Patients in the EU receiving lenalidomide

Milestones: Routine PSURs in line with DLP of the latest EURD list.

III.3 Summary Table of additional Pharmacovigilance activities

Pregnancy Prevention Programme Implementation

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Monitoring of Pregnancy prevention programme implementation (category 3 study) Status: Planned	Monitoring of implementation and the effectiveness of PPP	*Teratogenicity*	Routine PSURs in line with DLP of the latest EURD list	Data will be reviewed on an on-going basis as a part of signal detection and reported within PSURs with in-line with EURD list

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Teratogenicity	**Routine risk communication:** **SmpC** ***SmPC section 4.4. Special warnings and precautions for use*** ***SmPC section 4.6. Fertility, pregnancy and lactation*** ***SmPC section 4.8. Undesirable effects*** ***SmPC section 5.3. Preclinical safety data*** *These sections highlight the potential teratogenic effects of lenalidomide.* **PL** ***PL section 2*** *This document warns of the potential teratogenic effects of lenalidomide and the need to avoid pregnancy.* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** **SmPC** ***Section 4.3. Contraindications*** Lenalidomide is contraindicated in pregnant woman and in female with childbearing potential unless all the conditions of the Pregnancy Prevention Programme are met. ***Section 4.4. Special warnings and precautions for use*** This section highlights the potential teratogenic effects of lenalidomide. Stringent controls are required to ensure exposure of an unborn child to lenalidomide does not occur. These include: - Criteria for women of non-childbearing potential - Counselling - Contraception - Pregnancy testing - Precautions for men - Additional precautions - Reference to educational materials, prescribing and dispensing restrictions. **Other routine risk minimisation measures beyond the Product Information:** Pack size:

Safety concern	Routine risk minimisation activities
	The pack is based on a maximum 4-week supply of capsules to ensure that women with childbearing potential are required to obtain a new monthly prescription with a medically supervised pregnancy test. Legal status: Lenalidomide is subject to restricted medical prescription.
Serious Infection due to Neutropenia	**Routine risk communication:** **SmPC** ***SmPC section 4.8 Undesirable effects*** Listed as ADR. **PL** ***PL section 4*** This document warns that lenalidomide may cause neutropenia and infections and that if patient has, or has had HBV infection, lenalidomide may cause the virus to become active again. Viral infection, including herpes zoster (shingles) and recurrence of hepatitis B infection, are listed as possible side effects. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** **SmPC** ***Section 4.2 Posology and method of administration*** Dose reduction advice for neutropenia ***Section 4.4 Special warning and precautions for use*** Warning for neutropenia, and infection with or without neutropenia, and advice for monitoring patients, including blood testing for neutropenia. Advice that patients should report febrile episode promptly. Advice that HBV status should be established before initiating treatment with lenalidomide and advice to exercise caution when lenalidomide is used in patients previously infected with HBV. In addition, advice that the patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy. **PL** Advice to the doctor to check if patient has ever had hepatitis B infection prior to lenalidomide treatment. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Lenalidomide is subject to restricted medical prescription.
Second primary malignancies (SPM)	**Routine risk communication:** **SmPC**

Safety concern	Routine risk minimisation activities
	SmPC section 4.8 Undesirable effects Listed as ADRs. **PL** Informs patients on: - Risk of SPM - Need for the doctor to carefully evaluate benefit and risk, and - When lenalidomide is contraindicated **Routine risk minimisation activities recommending specific clinical measures to address the risk:** **SmPC** ***Section 4.4 Special warning and precautions for use*** This section highlights the risk of SPM, and advises standard cancer screening before and during lenalidomide use, with instigation of treatment as necessary. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Lenalidomide is subject to restricted medical prescription.
Cardiac failure	**Routine risk communication:** **SmPC** ***SmPC section 4.8 Undesirable effects*** Listed as ADRs. **PL** This document details the risks associated with lenalidomide use, their symptoms, and any actions to be taken by the patient. Symptoms of cardiac failure are listed as side effects. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Lenalidomide is subject to restricted medical prescription.
Cardiac arrhythmias	**Routine risk communication:** **SmPC** ***SmPC section 4.8 Undesirable effects*** Listed as ADRs. **PL**

Safety concern	Routine risk minimisation activities
	This document details the risks associated with lenalidomide use, their symptoms, and any actions to be taken by the patient. Symptoms of cardiac arrhythmia are listed as side effects. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Lenalidomide is subject to restricted medical prescription.
Ischaemic heart disease (including myocardial infarction)	**Routine risk communication:** **SmPC** ***SmPC section 4.8 Undesirable effects*** Listed as ADRs. **PL** This document details the risks associated with lenalidomide use, their symptoms, and any actions to be taken by the patient. Symptoms of ischaemic heart disease are listed as side effects. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** **SmPC** ***Section 4.4 Special warning and precautions for use*** This section highlights the possible occurrence of myocardial infarction, and advises monitoring of patients with known risk factors. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Lenalidomide is subject to restricted medical prescription.
Off label use	**Routine risk communication:** **SmPC** ***SmPC section 4.4 Special warning and precautions for use*** This section describes the collecting of detailed data relation to the indication in order to monitor closely the off-label use within the national territory. **PL** This document details the indications for which lenalidomide is approved. **Routine risk minimisation activities recommending specific clinical**

Safety concern	Routine risk minimisation activities
	measures to address the risk: None **Other routine risk minimisation measures beyond the Product Information:** Legal status: Lenalidomide is subject to restricted medical prescription.

V.2. Additional Risk Minimisation Measures

Pregnancy prevention programme (PPP)

Objectives:

The objective of the PPP is to minimise the risk of teratogenicity by:

- Ensuring that exposure of an unborn child to lenalidomide does not occur.
- Ensuring early alert to the physician of any pregnancies.
- Educating patients and HCPs on the safe use of lenalidomide
- Pregnancy testing and contraception requirements.
- A controlled access system to ensure that all appropriate measures have been performed prior to the drug being dispensed
- Follow-up on the effectiveness of the PPP

Rationale for the additional risk minimisation activity: Since there is increased risk of teratogenicity due to lenalidomide, additional measures are needed to minimize the risk of teratogenicity and provide education on the risk and on the necessary steps to prevent foetal exposure.

Target audience and planned distribution path:

The key elements of the lenalidomide PPP are set out below:

- Educational Programme:
    - Educational HCP's kit to include educational healthcare professional brochure, educational brochures for patients, patient card, risk awareness forms, and information on where to find latest SmPC.
- Therapy management
- Prescribing controls
- Dispensing controls
- Assessment

Targeted audience are the HCPs prescribing/dispensing this product and patients. Distribution will be performed according to national requirements.

Plans to evaluate the effectiveness of the interventions and criteria for success: The status of the implementation in each member states, any adaptations to the PPP, the results of any compliance measurements as process indicators undertaken in individual countries according to country

specific agreements with NCAs, reports of pregnancy exposure to be reviewed on an ongoing basis and summarized at the time of the PSUR overall and by country, outcome of pregnancy, modifications and corrective action will be taken accordingly. Pregnancy root cause analysis in cases of pregnancy exposure will be performed. Criteria for success: Outcome indicator - pregnancy exposures.

Additional HCP Educational Materials

- **Educational Healthcare Professional brochure**
- **Information on where to find latest SmPC**

Objectives: Raising awareness of healthcare professionals. To help healthcare professionals, who treat patients with lenalidomide, to understand the risk of teratogenicity and second primary malignancies associated with lenalidomide and appropriate management of patients to minimize the occurrence and the severity of this risks.

Rationale for the additional risk minimisation activity: Since there is increased risk of teratogenicity and second primary malignancies due to lenalidomide, additional measures are needed to understand the occurrence of the risks and the appropriate management.

Target audience and planned distribution path: Targeted audience are the physicians prescribing this product. Distribution will be performed according to national requirements.

Plans to evaluate the effectiveness of the interventions and criteria for success: AE reports will be reviewed on an ongoing basis, AE will be summarized at the time of the PSUR and modifications and corrective action will be taken accordingly. Criteria for success will be no increase in frequency or severity of the events as stated in the product information.

Additional Educational Materials for patients

- **Educational brochures for patients**
- **Patient card**
- **Risk awareness forms**

Objectives: Raising awareness of patients regarding the risk of teratogenicity.
Rationale for the additional risk minimisation activity: To understand the risk and the appropriate management of the risk.
Target audience and planned distribution path: Targeted audience are the patients who are prescribed lenalidomide. Distribution will be performed according to national requirements.
Plans to evaluate the effectiveness of the interventions and criteria for success: AE reports will be reviewed on an ongoing basis, AE will be summarized at the time of the PSUR and modifications and corrective action will be taken accordingly. Criteria for success will be no increase in frequency or severity of the events as stated in the product information.

Further details regarding above mentioned additional risk minimization measures are provided in the Annex 6.

V.3. Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Teratogenicity	**Routine risk minimisation measures:** Section 4.3 of SmPC: contraindicated in pregnant women and in women with childbearing potential unless all the conditions of the lenalidomide Pregnancy Prevention Programme 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. Sections 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 woman with childbearing potential are required to obtain a new monthly prescription with a medically supervised pregnancy test. Legal status: Lenalidomide is subject to restricted	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaires for risk of "teratogenicity". **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.

Safety concern	Risk minimisation measures	Pharmacovigilance activities

	medical prescription.
	
	Additional risk minimisation measures:
	- Lenalidomide Pregnancy Prevention Programme
	- Educational programme for healthcare professionals and patients:
	  o Educational HCP kit (Educational healthcare professional brochure, Educational brochures for patients, Patient card, Risk awareness forms and information on where to find latest SmPC)
	- 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
	  o Patient card to document childbearing status, counselling and pregnancy testing.	

Serious Infection due to Neutropenia	**Routine risk minimisation measures:** Section 4.2 of SmPC: dose reduction advice for neutropenia. Section 4.4 of SmPC**:** warning for neutropenia, and infection with or without neutropenia, and advice for monitoring patients, including blood testing for neutropenia. Advice that patients should report febrile episode promptly. Advice that HBV status should be	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaires for risk of "serious infection due to neutropenia" **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	established before initiating treatment with lenalidomide and advice to exercise caution when lenalidomide is used in patients previously infected with HBV. In addition, advice that the patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy. Section 4.8 of SmPC: listed as ADRs Advice to the doctor to check if patient has ever had hepatitis B infection prior to lenalidomide treatment. **Additional risk minimisation measures:** None.	
Second primary malignancies (SPM)	**Routine risk minimisation measures:** Section 4.4 of SmPC warning of second primary malignancies 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 Healthcare professional brochure	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaires for risk of "second primary malignancies" **Additional pharmacovigilance activities:** None
Cardiac failure	**Routine risk minimisation measures:** Listed as ADRs in Section 4. 8 of SmPC Listed in PL **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaires for risk of "cardiac failure" **Additional pharmacovigilance activities:** None
Cardiac arrhythmias	**Routine risk minimisation measures:** Listed as ADRs in Section 4. 8 of SmPC	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Listed in PL **Additional risk minimisation measures:** None.	**detection:** Specific adverse reaction follow-up questionnaires for risk of "cardiac arrythmias" **Additional pharmacovigilance activities:** None
Ischaemic heart disease (including myocardial infarction)	**Routine risk minimisation measures:** Myocardial infarction is included in Sections 4.4 and 4.8 of the SmPC. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaires for risk of "ischaemic heart disease (including myocardial infarction)" **Additional pharmacovigilance activities:** None
Off-label use	**Routine risk minimisation measures:** Collection of off-label use data detailed in Section 4.4. of SmPC **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Part VI: Summary of the risk management plan

Summary of risk management plan for Lenalidomide Krka (lenalidomide)

This is a summary of the risk management plan (RMP) for Lenalidomide Krka. The RMP details important risks of Lenalidomide Krka, how these risks can be minimised, and how more information will be obtained about Lenalidomide Krka 's risks and uncertainties (missing information).
Lenalidomide Krka's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Lenalidomide Krka should be used.
This summary of the RMP for Lenalidomide Krka 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 's RMP.

I. The medicine and what it is used for

Lenalidomide Krka is authorised for treatment of multiple myeloma, myelodysplastic syndromes, mantle cell lymphoma and follicular lymphoma (see SmPC for the full indication). It contains lenalidomide as the active substance and it is taken orally.
Further information about the evaluation of Lenalidomide Krka's benefits can be found in Lenalidomide Krka'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-previously-lenalidomide-krka-dd-novo-mesto.

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

Important risks of Lenalidomide Krka, together with measures to minimise such risks and the proposed studies for learning more about Lenalidomide Krka'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, 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 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. 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
	Second primary malignancies (SPM)
	Cardiac failure
	Cardiac arrhythmias
	Ischaemic heart disease (including myocardial infarction)
Important potential risks	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 minimisation measures	Routine risk minimisation measures Section 4.3 of SmPC: contraindicated in pregnant women and in FCBP unless all the conditions of the lenalidomide

Important identified risk: Teratogenicity	
	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: o Educational HCP kit (Educational healthcare professional brochure, Educational brochures for patients, Patient card, Risk awareness forms and information on where to find latest SmPC) - 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 o Patient card to document childbearing status, counselling and pregnancy testing.
Additional pharmacovigilance	Additional pharmacovigilance activities:

Important identified risk: Teratogenicity	
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. 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: Second primary malignancies (SPM)	
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 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.

Important identified risk: Second primary malignancies (SPM)	
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 Healthcare professional brochure

Important identified 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 None

Important identified 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 identified 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, MCL and FL.
Risk minimisation measures	Routine risk minimisation measures - Myocardial infarction is included in Sections 4.4 and 4.8 of the SmPC.

Important identified risk: Ischemic heart disease (including Myocardial Infarction)	
	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. 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.

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.

Part VII: Annexes

Annex 1 – EudraVigilance Interface

Not applicable.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones
Monitoring of Pregnancy Prevention Programme implementation (Category 3 study) Status: Planned	Monitoring of implementation and effectiveness of PPP	Teratogenicity	Routine PSURs in line with DLP of latest EURD list

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable.

Annex 4 - Specific adverse drug reaction follow-up forms

Specific adverse reaction follow-up questionnaires for the following safety concerns:	Follow-up Form Title
Teratogenicity	Pregnancy follow up forms: • Pregnancy Background (Patient or Partner of Patient) • Pregnancy Follow-up (Patient or Partner of Patient) • Pregnancy Outcome (Patient or Partner of Patient) • Infant Follow-up
Serious Infection due to Neutropenia	Neutropenia
Second Primary Malignancies (SPM)	Second Primary Malignancies

Cardiac failure	Cardiac failure
Cardiac arrhythmias	Cardiac arrhythmia and ECG Changes
Ischaemic heart disease (including myocardial infarction)	Myocardial infarction

Pregnancy follow-up questionnaires

Pregnancy Background

Event-Specific Questionnaire for HCP (Patient or Partner of Patient)

Telephone: _____

Fax: _____

Email: _____

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 ☐ AFRICAN-AMERICAN ☐ ASIAN ☐ OTHER, SPECIFY:	
Partner of Patient Information ☐ Not applicable			
DATE OF BIRTH:	ETHNICITY: ☐ WHITE ☐ AFRICAN-AMERICAN ☐ ASIAN ☐ OTHER, SPECIFY:		
Patient Treatment Information:			
LOT NO.:	EXPIRY DATE:	DOSE:	FREQUENCY:
ROUTE:	START DATE:	STOP DATE:	
INDICATI0N 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 deliveries:	No. of pre-term 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

If yes, in what week of pregnancy did the stillbirth or spontaneous abortion occur? Week:

Was there any birth defect noted? ? ☐ No ☐ Yes, if Yes please specify:

Relevant Medical History

☐ No ☐ Yes, if Yes please specify:			
MEDICAL HISTORY	DATE OF DIAGNOSIS	MEDICAL HISTORY	DATE OF DIAGNOSIS

Social History	
ALCOHOL ☐ NO ☐ YES, IF YES, AMOUNT/UNIT CONSUMED PER DAY:	
TOBACCO ☐ 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)	SERIOUS		ONSET DATE	STOP DATE/ ONGOING	CAUSAL RELATIONSHIP TO LENALIDOMIDE	
	YES/NO	SERIOUS CRITERIA[1]			YES/NO	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] □ [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 _____

Pregnancy Follow-up

Event-Specific Questionnaire for HCP (Patient or Partner of Patient)

Telephone:_____

Fax: _____

Email: _____

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 LENALIDOMIDE	
			YES/ NO	SERIOUS CRITERIA[1]	YES/ NO	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 _____

Pregnancy Outcome

Event-Specific Questionnaire for HCP (Patient or Partner of Patient)

Telephone:_____

Fax: _____

Email: _____

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: _____

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 Outcome			
	NO	YES	
Live Normal Infant	☐	☐	
Fetal Distress	☐	☐	
Intra-uterine Growth Retardation	☐	☐	
Neonatal Complications*	☐	☐	If Yes, please specify:
Birth Defect Noted?	☐	☐	If Yes, please 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 _____

Infant Follow-up

Event-Specific Questionnaire for Primary Care Physician or Pediatrician

Telephone:_____

Fax: _____

Email: _____

Date of assessment:_____

Age in months:

Weight (at the time of this assessment): lbs oz or kg_

Length:_____inches or _____cm

Name of Patient on lenalidomide:

Name of infant (if known):

Plese provide 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 lenalidomide 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)

Development 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	

SIGNATURE OF PERSON COMPLETING THIS FORM _____ DATE _____

NEUTROPENIA

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/MM/YYYY)			
Stop date (dd/MM/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.

Add diagnosis here→	Adverse event #1	Adverse event #2	Adverse event #3	Adverse event #4
Start date (DD/MM/YYYY)				
Stop date (DD/MM/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
	WBC					
	ANC					

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/MM/YYYY)	Stop date (DD/MM/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:

1. What treatment were given for the neutropenia? Please include dates. Did the patient receive G-CSF? GM-CSF? Please provide details.

2. Did your patient experience an infection in association with the neutropenia?
   ☐Yes ☐ No
   If yes, please provide location of the infection

3. Does the patient have a history of recurrent infection?
   ☐Yes ☐ No
   If yes, please explain.

4. Please provide the stage/classification of the patient's disease (specify) at the time of the infection.

5. Does your patient have a medical history of autoimmune disease, abnormal disease of spleen, bone marrow disease, etc.?

6. Has your patient received prior radiation therapy? If so, please provide treatment details including dates.

7. Does your patient have a medical history of cancer effecting bone marrow?

8. Please include culture / serology / bone marrow studies / x-ray for the event of infection.

Health Practitioner Name (Print)

Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:
Description of event: [narrative]

SECOND PRIMARY MALIGNANCIES (SPM)

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/MM/YYYY)			
Stop date (dd/MM/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.

Add diagnosis	Adverse event #1	Adverse event #2	Adverse event #3	Adverse event #4

here→				
Start date (DD/MM/YYYY)				
Stop date (DD/MM/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 regimen	Route of administration	Indication	Start date (DD/MM/YYYY)	Stop date (DD/MM/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:

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

Core Questions tor 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 lenalidomide 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 – length of time, number of cigarettes/day, age at starting, gender, Product smoked and depth of inhalation

☐ 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 poliposis)

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 g

Mouth and Oropharyngeal Cancer:

☐ History of alcohol use/smoking
☐ History of poor oral hygiene
☐ Chronic mucosal/gum irritation / ill-filling 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,
☐ 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]

CARDIAC ARRHYTHMIA and ECG Changes

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/MM/YYYY)			
Stop date (DD/MM/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	Adverse event	Adverse event	Adverse event #4

Add diagnosis here→	#1	#2	#3	
Start date (DD/MM/YYYY)				
Stop date (DD/MM/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					
	CPK-MB					
	Troponin					
	RBC					
	Hemoglobin					
	Metabolic Panel (specify)					
	Serum potassium					
	Serum magnesium					
	Phosphorus					
	Calcium					
	Uric acid					
	Creatinine					
	BUN					

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 any antiemetics.

Medication name	Daily dose and regimen	Route of administration	Indication	Start date (DD/MM/YYYY)	Stop date (DD/MM/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:

Please provide a brief description of the cardiac arrhythmia, or ECG change, including the type and the clinical signs/symptoms observed, including start and stop dates:

Please specify the type of arrhythmia/ECG change.

Clinical signs and symptoms, if present (if none please state)

Start date Stop date

Does this patient have a relevant cardiac history? If yes, please specify in box below. If no, please state.

Does this patient have a history of cardiac risk factors (e.g. hypertension, hyperlipidemia, hypercholesterolemia, diabetes, sepsis, obesity, smoking, renal disease, cardio respiratory problems)? If yes, please specify in the box below. If no, please state

Please provide the available results of the diagnostic workup (include dates of baseline, event onset, and resolution results)

Test Name	Pre-treatment results	AE onset results	AE resolution results
EKG findings			
Echocardiogram			
Chest x-ray			
Holter, Stress Test			

Please describe specific treatments and interventions of the arrhythmia

Health Practitioner Name (Print)

Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

CARDIAC FAILURE

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/MM/YYYY)			
Stop date (dd/MM/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.

Add diagnosis here→	Adverse event #1	Adverse event #2	Adverse event #3	Adverse event #4
Start date (DD/MM/YYYY)				
Stop date (DD/MM/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					
	Magnesium					
	Total CPK					
	CK-MB					
	Troponins					
	BNP					
	WBC					
	RBC					
	Platelets					
	Hemoglobin					
	Hematocrit					

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/MM/YYYY)	Stop date (DD/MM/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:

1.)Did the cardiac failure occur prior to therapy? □ Yes □ No

a. It the cardiac failure occurred prior to therapy, would you consider it an exacerbation?

□ Yes □ No

b. Please provide the date the exacerbation was diagnosed: _____

2) Please circle classification of cardiac failure:

a) Class I (mild) Patients with cardiac disease but without limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or angina pain

b) Class II (mild) Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina pain.

c) Class III (moderate) Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or angina pain.

d) Class IV (severe) Patients with cardiac disease resulting in the inability to carry on any physical activity without discomfort. Symptoms of heart failure or the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

Please provide results for EKG, echocardiogram, angiogram, CT scan, MRI and ejection fraction.

3) Did the patient receive any recent blood transfusions or IV infusions? □ Yes □ No

It yes, please specify what was transfused and provide the amount transfused with dates.

4) Does the patient have other cardiac history including congenital heart disease, coronary artery disease, cardiac stents, myocardial infarction, valvular heart disease, cardiomyopathy, endocarditis, or myocarditis?

5) Please provide any associated risk factors including history of hyperlipidemia, obesity, hypertension COPD, renal disease, diabetes, sepsis, substance abuse, and family history of heart disease.

6) Any exposure to other chemotherapeutic agents (previous and/or ongoing)? Please specify

7) Are there any concurrent events that contributed or led up to the cardiac failure? Please specify.

8) What treatments/interventions were provided to the patient tor the cardiac failure?

Health Practitioner Name (Print)

Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:
Description of event: [narrative]

MYOCARDIAL INFARCTION

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/MM/YYYY)			
Stop date (dd/MM/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.

Add diagnosis here→	Adverse event #1	Adverse event #2	Adverse event #3	Adverse event #4
Start date (DD/MM/YYYY)				
Stop date (DD/MM/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					
	Calcium					
	Magnesium					

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/MM/YYYY)	Stop date (DD/MM/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]

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

1. 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 prescribing (where appropriate, and in agreement with the National Competent Authority, dispensing) all healthcare professionals who intend to prescribe (and dispense) Lenalidomide Krka 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).
2. 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.
3. The MAH should agree 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.
4. The MAH should agree on the implementation of the controlled access programme in each Member State.

Key elements to be included

<u>The Educational Healthcare Professional's Kit</u>

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

Educational Healthcare Professional brochure

- Brief background on lenalidomide
- Maximum duration of treatment prescribed
    - 4 weeks for women with childbearing potential
    - 12 weeks for men and women without childbearing potential
- The need to avoid foetal exposure due to teratogenicity of lenalidomide in animals and the expected teratogenic effect of lenalidomide in humans
- Guidance on handling the blister or capsule of lenalidomide for healthcare professionals and caregivers
- Obligations of the healthcare professionals who intend to prescribe or dispense Lenalidomide Krka
    - Need to provide comprehensive advice and counselling to patients

- That patients should be capable of complying with the requirements for the safe use of lenalidomide
- Need to provide patients with appropriate patient educational brochure, patient card and/or equivalent tool

- Safety advice relevant to all patients
  - Description of risk of SPM
  - Local country specific arrangements for a prescription for lenalidomide 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 Lenalidomide Krka
- 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 lenalidomide
    - The physician prescribing lenalidomide 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 lenalidomide 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 lenalidomide 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 Lenalidomide Krka treatment

    - That if his partner becomes pregnant whilst he is taking Lenalidomide or shortly after he has stopped taking lenalidomide he should inform his treating doctor immediately
- Requirements in the event of pregnancy
    - Instructions to stop Lenalidomide 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 patients 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 lenalidomide is teratogenic in animals and is expected to be teratogenic in humans
- Description of the patient card and its necessity
- Guidance on handling Lenalidomide Krka for patients, caregivers and family members
- National or other applicable specific arrangements for a prescription for lenalidomide to be dispensed
- That the patient must not give Lenalidomide Krka 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 Lenalidomide Krka 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 lenalidomide
    - The physician prescribing lenalidomide 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 lenalidomide 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 Lenalidomide Krka 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 for 7 days following discontinuation of Lenalidomide Krka 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 lenalidomide 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 lenalidomide. 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 lenalidomide
- that she understands the need to avoid lenalidomide during pregnancy and to apply effective contraceptive measures without interruption, at least 4weeks before starting treatment, throughout the entire duration of treatment, and at least 4weeks 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 Lenalidomide Krka
    - the physician prescribing Lenalidomide Krka 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 Lenalidomide Krka 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 Lenalidomide Krka
- 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 Lenalidomide Krka
    - 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 lenalidomide 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 a 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 Lenalidomide Krka
    - that he should return the unused capsules to the pharmacist at the end of treatment

Annex 7 - Other supporting data (including referenced material)

Not applicable.

Annex 8 – Summary of changes to the risk management plan over time

Version	**Approval date** **Procedure**	**Change**
0.4	At the time of authorisation EMA/H/C/005348 10/12/2020	Not applicable
1.1	Variation procedure EMA/H/C/005348/IB/0007/G 02/07/2024	<u>Pharmacovigilance Plan:</u> - update of all follow-up questionnaires, - update of Other forms of routine pharmacovigilance activities - Initial Pregnancy Report Form deleted <u>Risk minimisation measures</u> - update of PPP information, Educational brochure for HCP and Educational brochure for patients <u>Annexes</u> - Annex 4: Update of all follow-up questionnaires - Annex 6: Educational HCP brochure – update of information, deletion of Pregnancy reporting form, deletion of Adverse event reporting form; Addition of risk awareness forms