RISK MANAGEMENT PLAN
For
Lenalidomide
Version 1.4

RMP Version to be Assessed as Part of this Application:

RMP Version Number	1.4
Data Lock Point for this RMP	15-Jan-2024
Date of Final Sign Off	08-Jul-2024
Rationale for Submitting an Updated RMP	The RMP has been updated in line with Revlimid RMP version 39.1 (DLP 24-May-2023, date of sign off 13-Jul-2023), EMEA Type IB variation report for Lenalidomide Mylan EMEA/H/C/005306/IB/0016/G dated 14-May-2024 and EMA Rapporteur's request dated 04-Jul-2024
Summary of Significant Changes in this RMP	The RMP has been updated in accordance with Revlimid RMP version 39.1 (DLP 24-May-2023, date of sign off 13-Jul-2023), EMEA Type IB variation report for Lenalidomide Mylan EMEA/H/C/005306/IB/0016/G dated 14-May-2024 and Part III and Part VI: II.C were amended as per EMA Rapporteur's request dated 04-Jul-2024

Other RMPs under evaluation:

RMP Version Number	1.3
Submitted On	13-Jun-2024
Procedure Number	EMEA/H/C/005306/IB/0016/G

Details of the Current RMP:

Version Number	1.1
Approved with Procedure	EMEA/H/C/0005306/IB/0004/G
Date of Approval (Opinion Date)	19-Jul-2021

QPPV name: Dr Eiko Soehlke, MD MPH,

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse drug reaction
AML	Acute Myeloid Leukemia
ASCT	Autologous stem cell transplantation
ATC	Anatomical Therapeutic Chemical Classification System
CHD	Chronic heart disease
CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual recognition and Decentralised Procedures – Human
CVD	Cardiovascular disease
DCP	Decentralised Procedure
DDD	Daily Defined Dose
DHPC	Direct Healthcare Professional Communication
DLP	Data Lock Point
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
EURD	European Union Reference Date
HBV	Hepatitis B virus
HCP	Healthcare Professional
ICSR	Individual Case Safety Report
INN	International non-proprietary name
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
MCL	Mantle cell Lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
MRP	Mutual Recognition Procedure
NCA	National Competent Authority
NDMM	Newly diagnosed multiple myeloma
NMSC	Non-melanoma skin cancer

PAC	Patient Alert Card
PL	Package leaflet
PPP	Pregnancy Prevention Programme
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PTC	Patient treatment course
PTD	Patient treatment Days
PTM	Patient treatment Months
PTY	Patient treatment Years
PVA	Pharmacovigilance Agreement
QPPV	Qualified Person for Pharmacovigilance
SPC	Summary of Product Characteristics
SPM	Second Primary Malignancy
TFR	Tumour Flare Reaction
WHO	World Health Organization

PART I: PRODUCT(S) OVERVIEW

Table 1: Part 1.1-Product Overview

Active Substance(s) (INN or Common Name)	Lenalidomide
Pharmacotherapeutic Group(s) (ATC Code)	Immunosuppressants, Other immunosuppressants. ATC code: L04AX04
Marketing Authorisation Holder	Mylan Ireland Limited
Medicinal Products to Which this RMP Refers	01
Invented Name(s) in the European Economic Area (EEA)	Lenalidomide Mylan
Marketing Authorisation Procedure	Centralized EMEA/H/C/0005306
Brief Description of the Product	Lenalidomide belongs to class of immunosuppressants. Mechanism of action The lenalidomide mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including MM plasma 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 cells, 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. 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 the presence of lenalidomide, cereblon binds substrate proteins Aiolos and Ikaros which are lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation resulting in cytotoxic and immunomodulatory effects.

Hyperlink to the Product Information:	PI available in section 1.3.1 of the dossier
Indication(s) in the EEA **Current**	Multiple myeloma Lenalidomide Mylan as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation. Lenalidomide Mylan as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant. Lenalidomide Mylan in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy. Myelodysplastic syndromes Lenalidomide Mylan as monotherapy is indicated for the treatment of adult patients with transfusion-dependent anaemia 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. Mantle cell lymphoma Lenalidomide Mylan as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma. Follicular lymphoma Lenalidomide Mylan in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3a).
Dosage in the EEA Current	Posology *Newly diagnosed multiple myeloma (NDMM)* Lenalidomide in combination with dexamethasone until disease progression in patients who are not eligible for transplant

	Lenalidomide treatment must not be started if the 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. <u>Lenalidomide in combination with bortezomib and dexamethasone followed by lenalidomide and dexamethasone until disease progression in patients who are not eligible for transplant.</u> 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. <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. Lenalidomide maintenance in patients who have undergone transplantation (ASCT) Lenalidomide maintenance should be initiated after adequate haematologic recovery following ASCT in patients without evidence of progression. Lenalidomide must not be started if the Absolute Neutrophil Count (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. *Multiple myeloma with at least one prior therapy* 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. *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. *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. *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/m2 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. *Tumour flare reaction* Lenalidomide may be continued in patients with Grade 1 or 2 tumour flare reaction (TFR) without interruption or modification, at the physician's discretion. In patients with Grade 3 or 4 TFR, withhold treatment with lenalidomide until TFR resolves to ≤ Grade 1and patients may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR (see section 4.4). 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, 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.
Pharmaceutical Form(s) and Strengths Current	Lenalidomide Mylan 2.5 mg, hard capsules Lenalidomide Mylan 5 mg, hard capsules Lenalidomide Mylan 7.5 mg, hard capsules Lenalidomide Mylan 10 mg, hard capsules Lenalidomide Mylan 15 mg, hard capsules Lenalidomide Mylan 20 mg, hard capsules Lenalidomide Mylan 25 mg, hard capsules
Is the Product 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

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

This is a MAA for a generic medicine in which the safety concerns available in the RMP for the reference medicinal product have been adopted by the MAH (EPAR-Risk management plan summary of Revlimid dated 11-Jun-2019).

Table 2: SVII- Summary of safety concerns

Summary of Safety Concerns	
Important Identified Risks	• Teratogenicity • Serious infection due to neutropenia • Second primary malignancies (SPM) <u>Important Identified Risk Related to Indication/Target Population</u>: • For FL (follicular lymphoma): Tumour Flare Reaction (TFR)
Important Potential Risks	• Cardiac failure • Cardiac arrhythmias • Ischaemic heart disease (including myocardial infarction)

Summary of Safety Concerns	
	• Off-label use
Missing Information	• None

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable as all risks from reference product RMP have been considered in this RMP.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable as all risks from reference product RMP have been considered in this RMP.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Update from RMP version 0.6 to 1.1 via variation EMEA/H/C/005306/IB/0004/G: With the addition of the indication Myelodysplastic syndromes and MCL (Mantle cell lymphoma), the Important identified risk "For FL (follicular lymphoma): Tumour Flare Reaction (TFR)" from the current approved RMP 0.6 has been updated to "For MCL (Mantle cell lymphoma) and FL (follicular lymphoma): Tumour Flare Reaction (TFR)", in line with Revlimid (reference substance) RMP updated on 15-Jan-2020 published on EMA website.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Not applicable as this RMP for lenalidomide follows the same safety concerns as the safety concerns of the reference substance RMP.

SVII.3.2. Presentation of the Missing Information

Not applicable as this RMP for lenalidomide follows the same safety concerns as the safety concerns of the reference substance RMP.

Part II: Module SVIII - Summary of the Safety Concerns

Table 3: SVIII- Summary of safety concerns

Important Identified Risks	• Teratogenicity • Serious infection due to neutropenia • Second primary malignancies (SPM) Important Identified Risk Related to Indication/Target Population: • For MCL (Mantle cell lymphoma) and FL (follicular lymphoma): Tumour Flare Reaction (TFR)
Important Potential Risks	• Cardiac failure

	• Cardiac arrhythmias • Ischaemic heart disease (including myocardial infarction) • Off-label use
Missing Information	None

PART III: PHARMACOVILIGANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

The Pharmacovigilance System Master File contains details of the system and processes that the MAH has in place to identify and characterize the risks recognised in the safety specification.

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities only.

Specific adverse reaction follow-up questionnaires for risks:

- Teratogenicity
- Serious infection due to neutropenia
- Second primary malignancies (SPM)
- For MCL (Mantle cell lymphoma) and FL (follicular lymphoma): TFR
- Cardiac failure
- Cardiac arrhythmias
- Ischaemic heart disease (including myocardial infarction)
- Off-label use

The forms are provided in Annex 4 of the RMP.

Other Forms of Routine Pharmacovigilance Activities

Expedited Reporting and Follow-up of Pregnancy:

The pregnancy capture and follow-up procedure is 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.

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 Educational Materials in the Educational HCP's Kit make reference to the requirement to report all suspected pregnancies to Viatris 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 by Viatris are entered into company's 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 are immediately processed. EU Health Authorities are notified of these reports.

Follow-up

All reports of pregnancies are followed up.

In general, for reports of drug exposure during pregnancy (maternal exposure and paternal exposure), follow-up should be attempted three (3) months after the estimated delivery date (EDD) within 30 calendar days.

If the EDD is unknown, a follow-up attempt should be made nine (9) months of the initial report within 30 calendar days. A second follow-up attempt may be considered in order to obtain missing, incomplete or supplementary information. The second attempt should be made one month after the first within 30 calendar days. In the case of lenalidomide, pregnancy cases will be followed up according to the timelines specified in RMP annex 4 and in line with the company's processes.

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

In general, for reports of drug exposure during pregnancy (maternal exposure and paternal exposure), follow-up should be attempted three (3) months after the estimated delivery date (EDD) within 30 calendar days.

If the EDD is unknown, a follow-up attempt should be made nine (9) months of the initial report within 30 calendar days. A second follow-up attempt may be considered in order to obtain missing, incomplete or supplementary information. The second attempt should be made one month after the first within 30 calendar days. In the case of lenalidomide, pregnancy cases will be followed up according to the timelines specified in RMP annex 4 and in line with the company's processes.

Root Cause of Failure of Pregnancy Prevention Programme

Detailed description of the root cause of failure of PPP will be included in the pregnancy-related follow up forms and captured in the case narrative.

Regulatory Reporting of Pregnancies

All initial pregnancy reports and follow-up information are reported on an expedited basis within 15 days. Should any suspected teratogenic effect be reported following treatment with lenalidomide, this is expedited immediately.

Compliance with the PPP should be monitored in each member state.

In line with the requirements set out for the innovator product, the MAH shall agree with each member state prior to marketing the set-up of national measures.

An Analysis of Adverse Drug Reactions of Special Interest within the Required PSURs

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

The pregnancy capture and follow-up procedure is detailed above. Physicians are encouraged or required as per local legislation to report pregnancies to the MAH and/or the NCA.

Study Title	Monitoring of Pregnancy Prevention Programme implementation
Category	3
Rationale and Study Objectives	Monitoring of implementation of PPP
Study Design	Additional monitoring of the implementation of the PPP is carried out on a country basis in agreement with relevant NCA.
Study Populations	Patients in EU receiving MAH's lenalidomide
Milestones	Ongoing; In line with the EURD PSUR

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 4: Part III.2- On-going and planned additional pharmacovigilance activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
Monitoring of Pregnancy Prevention Programme implementation	Monitoring of implementation of PPP	Teratogenicity	Routine PSURs in line with EURD list	Ongoing; In line with DLP of the latest EURD list

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMISATION MEASURES

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product (Revlimid, by Bristol-Myers Squibb Pharma EEIG).

V.1 Routine Risk Minimisation Measures

Table 5: Part V.1- Description of routine risk minimisation measures by safety concern

Safety Concern	Routine Risk Minimisation Activities
Teratogenicity	Routine risk communication: SmPC section 4.3, 4.4, 4.6, 4.8 and 5.3 PL section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC sections 4.3 and 4.4 PL section 2 Other risk minimisation measures beyond the Product Information: Medicine's legal status: lenalidomide is subject to restricted medical prescription
Serious infection due to neutropenia	Routine risk communication: SmPC section 4.2, 4.4, 4.8. PL sections 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.4 PL section 2 Other risk minimisation measures beyond the Product Information: Medicine's legal status: lenalidomide is subject to restricted medical prescription
Second Primary Malignancies	Routine risk communication: SmPC section 4.4, 4.8. PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.4 Other risk minimisation measures beyond the Product Information:

Safety Concern	Routine Risk Minimisation Activities
	Medicine's legal status: lenalidomide is subject to restricted medical prescription
For MCL (Mantle cell lymphoma) and FL (follicular lymphoma): TFR	Routine risk communication: SmPC section 4.2, 4.4, 4.8. PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.2 and 4.4 PL section 2 Other risk minimisation measures beyond the Product Information: Medicine's legal status: lenalidomide is subject to restricted medical prescription
Cardiac failure	Routine risk communication: SmPC section 4.8. PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other risk minimisation measures beyond the Product Information: Medicine's legal status: lenalidomide is subject to restricted medical prescription
Cardiac arrhythmias	Routine risk communication: SmPC section 4.8. PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other risk minimisation measures beyond the Product Information: Medicine's legal status: lenalidomide is subject to restricted medical prescription

Safety Concern	Routine Risk Minimisation Activities
Ischaemic heart disease (including myocardial infarction)	Routine risk communication: SmPC section 4.4, 4.8 PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC sections 4.4 Other risk minimisation measures beyond the Product Information: Medicine's legal status: lenalidomide is subject to restricted medical prescription
Off-label use	Routine risk communication: SmPC section 4.4 Other risk minimisation measures beyond the Product Information: Medicine's legal status: lenalidomide is subject to restricted medical prescription

V.2 Additional Risk Minimisation Measures

This medicine has additional risk minimisation measures for the risks Teratogenicity, Second primary malignancies (SPM) and for MCL (Mantle cell lymphoma) and FL (follicular lymphoma): TFR (tumour Flare reaction).

The additional risk minimisation measures consist of:

- For risk Teratogenicity - PPP (pregnancy prevention programme), HCP and Patient educational materials and patient card
- For risk Second primary malignancies (SPM) – HCP and Patient educational materials
- For risk TFR – HCP educational material

Pregnancy Prevention Programme:

Objectives:

- 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:

To minimize the risk of teratogenicity and provide education on the risk and the necessary steps to prevent foetal exposure.

Target Audience and Planned Distribution Path:

Educational material	Target Audience
Educational health care professional's brochure	HCPs
Educational brochures for patients	Patients
Patient cards	Patients

The MAH shall agree the details of a controlled access system 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 Mylan 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).

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.

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.

The MAH should agree on the implementation of the controlled access programme in each Member State.

Key elements of the PPP and educational materials are described in Annex 6.

Plans for Evaluating the Effectiveness of the Interventions and Criteria for Success:

Effectiveness of additional RMMs will be evaluated on annual basis after MA approval. The criteria of success (pregnancy exposure) will be reviewed and detailed on an annual basis through PSUR, by assessing:

- status of the implementation in each Member State,
- 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 summarised at the time of the PSUR overall and by country,
- root causes for pregnancy exposure as per pregnancy report form,
- outcome of pregnancy,
- modifications and corrective action taken accordingly

Criteria for Success:
Outcome indicator: pregnancy exposures
Results of Effectiveness Evaluation

After evaluation of all information available to Viatris, including ICSRs from Viatris's global safety database, global literature, PSUR outcome, outcome of signal detection activities, National Competent authority websites, results of interventional and non-interventional studies and EudraVigilance data, the risk minimization measures in place for this risk have been considered adequate. The benefit-risk profile of the product remains favourable and unchanged and no further change in the risk minimization measures is needed.

Patient Educational Materials:

- Educational brochure for patients
- Patient card
- Risk awareness forms

Objectives:

Provision of information to patients for the risks of:

- Teratogenicity
- SPM

Rationale for the additional risk minimisation activity:

The MAH considers it is necessary to educate patients about specific risks, their early symptoms and the best course of action to be taken when these appear beyond the recommendation contained in the Product Information.

Target audience and planned distribution path:

Patients who are prescribed lenalidomide and the planned distribution path is the provision of patient brochure by healthcare professionals. The MAH shall agree the details of a controlled access system with the National Competent Authorities.

Plans for evaluating the effectiveness of the interventions and criteria for success:

Effectiveness of additional RMMs will be evaluated on annual basis after MA approval.

Criteria for Success:

Outcome Indicator: Frequency and severity of events. No significant increase in frequency of reports in the postmarketing setting versus the SmPC.

Results of effectiveness evaluation

After evaluation of all information available to Viatris, including ICSRs from Viatris's global safety database, global literature, PSUR outcome, outcome of signal detection activities, National Competent authority websites, results of interventional and non-interventional studies and EudraVigilance data, the risk minimization measures in place for this risk have been considered adequate. The benefit-risk profile of the product remains favourable and unchanged and no further change in the risk minimization measures is needed.

HCP Educational Materials:

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

Objectives:

HCP Educational materials to be provided to prescribing physicians and pharmacists for the risks of:

- Teratogenicity
- SPM
- TFR

Rationale for the additional risk minimisation activity:

The MAH considers it is necessary to educate HCPs about specific risks, and/or their early symptoms and/or the best course of action to be taken when these appear beyond the recommendation contained in the Product Information.

Target audience and planned distribution path:

HCPs who prescribe lenalidomide.

The MAH shall agree the details of a controlled access system with the National Competent Authorities.

Key elements of the educational materials are described in Annex 6 - Details of Proposed Additional Risk Minimisation Activities (If Applicable).

Plans for evaluating the effectiveness of the interventions and criteria for success:

Effectiveness of additional RMMs will be evaluated on annual basis after MA approval.

Criteria for Success:

Outcome Indicator: Frequency and severity of events. No significant increase in frequency of reports in the post marketing setting as presented in the SmPC.

Results of effectiveness evaluation

After evaluation of all information available to Viatris, including ICSRs from Viatris's global safety database, global literature, PSUR outcome, outcome of signal detection activities, National Competent authority websites, results of interventional and non-interventional studies and EudraVigilance data, the risk minimization measures in place for this risk have been considered adequate. The benefit-risk profile of the product remains favourable and unchanged and no further change in the risk minimization measures is needed.

Rationale for Proposing to Remove Additional Risk Minimisation Measures:

Not applicable

V.3 Summary Table of Pharmacovigilance and Risk Minimisation Activities by Safety Concern

Table 6: 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 minimization measures: • SmPC sections 4.3, 4.4, 4.6, 4.8 and 5.3 • PL section 2 and 4 Additional risk minimisation measures: • Pregnancy prevention programme • HCP and Patient educational materials • Risk awareness forms • Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up forms for teratogenicity Additional pharmacovigilance activities: Monitoring of implementation and effectiveness of the PPP in each member states will be done in routine PSURs in line with EURD list
Serious infection due to neutropenia	Routine risk minimization measures • SmPC sections 4.2, 4.4, 4.8 • PL sections 2 and 4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for neutropenia Additional pharmacovigilance activities: None
Second Primary Malignancies	Routine risk minimization measures • SmPC sections 4.4 and 4.8 • PL section 4 Additional risk minimisation measures: • HCP and patient educational materials	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for Second primary malignancies Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
For MCL (Mantle cell lymphoma) and FL (follicular lymphoma): TFR	Routine risk minimization measures • SmPC sections 4.2, 4.4, 4.8 • PL sections 2 and 4 Additional risk minimisation measures: • HCP educational material	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for TFR Additional pharmacovigilance activities: None
Cardiac failure	Routine risk minimization measures • SmPC section 4.8 • PL section 4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for Cardiac failure Additional pharmacovigilance activities: None
Cardiac arrhythmias	Routine risk minimization measures • SmPC section 4.8 • PL section 4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for Cardiac arrythmias and ECG changes Additional pharmacovigilance activities: None
Ischaemic heart disease (including myocardial infarction)	Routine risk minimization measures • SmPC sections 4.4 and 4.8 • PL section 4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for Myocardial infarction

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		Additional pharmacovigilance activities: None
Off- label use	Routine risk minimization measures • SmPC section 4.4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for Off-label use Additional pharmacovigilance activities: None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Lenalidomide Mylan (lenalidomide)

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

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

This summary of the RMP for Lenalidomide Mylan should be read in the context of all the information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

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

I. The Medicine and What it is Used For

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

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

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

Lenalidomide Mylan as monotherapy is indicated for the treatment of adult patients with transfusion-dependent anaemia 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.

Lenalidomide Mylan as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma.

Lenalidomide Mylan in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3a).

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

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

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

Important risks of Lenalidomide Mylan, together with measures to minimise such risks and the proposed studies

for learning more about Lenalidomide Mylan's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimises its risks.

Together, these measures constitute routine risk minimisation measures.

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

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

II.A List of Important Risks and Missing Information

Important risks of Lenalidomide Mylan are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken by patients. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Lenalidomide Mylan. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine/use in special patient populations etc.);

Table 7: Part VI.1- Summary of safety concerns

List of Important Risks and Missing Information	
Important Identified Risks	• Teratogenicity • Serious infection due to neutropenia • Second primary malignancies (SPM) Important Identified Risk Related to Indication/Target Population: • For MCL (Mantle cell lymphoma) and FL (follicular lymphoma): Tumour Flare Reaction (TFR)
Important Potential Risks	• Cardiac failure • Cardiac arrhythmias • Ischaemic heart disease (including myocardial infarction) • Off-label use

Missing Information	• None

II.B Summary of Important Risks

Table 8: Part VI.2- Teratogenicity

Evidence for Linking the Risk to the Medicine	Lenalidomide is structurally related to thalidomide, which is known to cause serious birth defects and death of the foetus. In nonclinical studies, lenalidomide induced malformations similar to those described with thalidomide. Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy.
Risk Factors and Risk Groups	The 'at risk' group comprises females of child bearing potential or female partners of male patients treated with lenalidomide and there are no risk factors
Risk Minimisation Measures	Routine risk minimisation measures • Section 4.3 of SmPC: Contraindicated in pregnant women and in females of childbearing potential unless all the conditions of the pregnancy prevention programme are met. • Section 4.4 of SmPC: Warnings and Precautions for use a. Criteria for women of non-childbearing potential b. Counselling c. Contraception d. Pregnancy testing e. Precautions for men f. Additional precautions g. Reference to educational materials, prescribing and dispensing restrictions. • Section 4.6 of SmPC: Fertility, pregnancy and lactation. • Sections 4.8 and 5.3 of SmPC: The potential teratogenic effects of lenalidomide are highlighted. • Pack size: The pack is based on a maximum 4-week supply of capsules to ensure that females of 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. **Additional risk minimisation measures** • Pregnancy prevention programme (PPP) • HCP and patient educational materials (HCP and Patient brochures, risk awareness forms and information where to find the latest SmPC) • Patient card to document childbearing status, counselling and pregnancy testing.

Table 9: Part VI.3- Serious Infection due to Neutropenia

Evidence for linking the risk to the medicine	In clinical trials conducted for the originator product, neutropenia has been reported as a consequence of lenalidomide treatment; ≥ Grade 3 and ≥ Grade 4 infections have occurred in the context of neutropenia (any grade).
Risk factors and risk groups	Haematological malignancies by themselves or by virtue of their therapeutic strategies, chemotherapy, radiation or haematopoietic stem cell transplant put patients at risk of infections. The introduction of stem cell transplantation and novel anti-myeloma agents has improved the outcome of patients with MM. These advances have transformed MM into a chronic condition, with multiple relapses and salvage therapies, all of which results in cumulative immunosuppression and higher risk of infection. For example, application of stem cell transplantation has broadened the spectrum of infection to include those caused by Clostridium difficile, cytomegalovirus, and opportunistic moulds. Risk factors include myeloma-related innate immunodeficiency, which involves various arms of the immune system and includes B-cell dysfunction (manifested as hypogammaglobulinemia). Polyclonal hypogammaglobulinemia has been classically associated with infection by encapsulated bacteria, such as Streptococcus pneumoniae and Haemophilus influenzae. Myeloma and treatment-associated organ dysfunctions and comorbidities also increase the risk of infection. These dysfunctions and comorbidities include (1) renal failure (cast nephropathy, hypercalcemia, deposition disease, and others), respiratory compromise, caused by collapse of thoracic vertebra and opiate therapy (which may depress the central nervous system) given to patients with painful fractures (3), severe alimentary mucosal damage (caused by chemotherapy, radiation therapy, or graft-versus-host disease) (4) hyperglycemia induced by dexamethasone (5) transfusional iron overload and (6) the multisystem involvement by myeloma-associated deposition diseases (AL-amyloidosis and light chain deposit disease). Indeed, levels of CD4+ T cells, particularly naive and activated subsets, decrease significantly with increasing cycles of chemotherapy, a decrease strongly associated with opportunistic infections. Finally, myeloma typically affects an older population, with a median age of 62 to 73 years. These patients frequently experience an age-related decline in physiologic reserve of various organs and from other age-related conditions, including frailty, geriatric syndromes, cognitive dysfunction, and social isolation, all of which may increase the risk of infection. Lenalidomide treatment in combination with dexamethasone in MM patients with at least one prior therapy is associated with a higher incidence of neutropenia compared to placebo-dexamethasone treated patients. The combination of lenalidomide with melphalan and prednisone in clinical trials of NDMM patients is associated with a higher incidence of Grade 4 neutropenia than MPp+p treated patients. The proportion of patients who experienced Grade 3 or 4 myelosuppression in one study of lenalidomide-treated patients with MM was significantly higher for patients who had prior high-dose chemotherapy and stem cell transplantation, compared with those that did not. Impairment of antibody

	response, neutropenia, treatment with glucocorticoids, and reduction of normal Ig all increase the likelihood of infection. While a much greater proportion of lenalidomide/dexamethasone patients experienced neutropenia relative to placebo/dexamethasone patients, this increased risk did not translate into an infection risk of the same magnitude in either the total study population or in the study population restricted to Grade 3 or 4 toxicities. Lenalidomide treatment in MDS patients is associated with a higher incidence of Grade 3 or 4 neutropenia compared with patients on placebo. In patients with MDS, those experiencing neutropenia while receiving lenalidomide may be at increased risk for infections.
Risk minimisation measures	Routine risk minimisation measures • section 4.2 of SmPC: Dose reduction advice for neutropenia. • section 4.4 of SmPC: Warning of neutropenia, and infection with or without neutropenia and advice for monitoring patients, including blood testing for neutropenia. Advice regarding establishing HBV status before treatment, use in patients previously infected with HBV and monitoring for signs and symptoms of active HBV infection throughout therapy. • Listed as ADR in section 4.8 of SmPC. • Advice to patients in PL, including that the doctor is advised to check if the patient has ever had hepatitis B infection prior to starting lenalidomide treatment. Additional risk minimisation measures • Not applicable as there are no additional risk minimisation measures for this safety concern

Table 10: Part VI.4- Second Primary Malignancy

Evidence for linking the risk to the medicine	In clinical trials, AML and B-cell malignancies have been reported in patients treated with lenalidomide. Based on clinical trial data, lenalidomide may increase the risk of NMSC. Patients with multiple myeloma also have an increased risk of NMSC. Patients treated with lenalidomide may be at increased risk of developing new cancers. The reason is not clear, but further investigations are being undertaken for the originator product.
Risk factors and risk groups	MDS Populations (Haematologic Malignancies) A study to identify prognostic factors for progression to leukaemia (LFS) and OS was reported by Malcovati. Four hundred seventy-six patients first diagnosed with de novo MDS between 1992 and 2002 were evaluated. In one of the earliest studies to report the negative effects of developing a transfusion requirement, Malcovati reported an increased risk associated with transfusion burden when analysed as a time-dependent covariate in a combined group of patients with RA, RARS or MDS with del(5q) (HR = 3.46).

	Further development of the WPSS a learning cohort of 426 Italian MDS patients and a validation cohort of 193 German MDS patients was reported by Malcovati and colleagues. In a multivariable analysis of the Italian patients stratified by WHO subgroups, cytogenetics (HR = 1.48) and transfusion requirement (HR = 2.53) significantly affected OS and risk of AML (HR = 1.3 and HR = 2.4, respectively). These findings were corroborated in the subsequent multivariable analysis of German MDS patients stratified by WHO subgroups, with cytogenetics (HR = 1.84) and transfusion dependency (HR = 1.85) and risk of AML (HR = 2.27 and HR = 2.25, respectively). Mallo reported the results of a cooperative study designed to assess prognostic factors for OS and progression to AML in 541 patients with de novo MDS and del 5q. In multivariate analyses the most important predictors of both OS and AML progression were number of chromosomal abnormalities ($p < 0.001$ for both outcomes), platelet count ($p < 0.001$ and $p = 0.001$, respectively) and proportion of bone marrow blasts ($p < 0.001$ and $p = 0.016$, respectively). Transfusion burden was not addressed in this study. Knuendgen assessed the risk of AML progression and death in 295 lenalidomide-treated MDS-003 and MDS-004 patients versus 125 MDS patients with del 5q from a large multicentre registry who had received best supportive care only including ESAs. In the final multivariate Cox proportional hazard models, lenalidomide treatment was not associated with progression to AML (HR 0.939; $p = 0.860$). Significant factors associated with an increased risk of AML progression were complex cytogenetics (del 5q plus > 1 abn; HR 3.627; $p = 0.002$), bone marrow blasts 5% to 10% (HR 2.215; $p = 0.016$), and higher transfusion burden (HR 1.097 [10% increase in risk per unit at baseline]; $p = 0.029$). Higher haemoglobin levels were associated with a reduced risk (HR 0.857; $p = 0.054$). Regarding survival, lenalidomide treatment was associated with a reduced risk of death (HR 0.597; $p = 0.012$). Other factors associated with decreased mortality were higher haemoglobin levels (HR 0.883; $p = 0.028$), higher platelet counts (HR 0.999; $p = 0.035$), and female sex (HR 0.598; $p = 0.002$). Higher transfusion burden (HR 1.056; $p = 0.037$) and age (HR 1.049; $p < 0.001$) increased the risk of death. Mutations in the TP53 gene have been well described as a poor prognostic variable and associated with chemotherapy resistance in a wide variety of malignancies including high-risk MDS and AML. MCL Population (Haematologic Malignancies) There is no information available. NMSC Risk factors for NMSC include: increased sun or ultraviolet radiation exposure; physical factors such as fair skin, red or blond hair, and light eye colour; chemical carcinogens such as, arsenic, tobacco, and oral methoxsalen; ionising radiation; and previous history of NMSC.

	Prolonged survival as a result of improved therapies As previously noted, the 5-year relative survival among MM patients has increased from 24.6% among patients first diagnosed in 1975 to 1977 to 44.9% among patients first diagnosed between 2003 and 2009. Due to improvements in the care of patients with cancer, the number of cancer survivors has been increasing in recent years. Increased longevity increases the risk of developing second malignancy, including NMSC. Immunosuppression associated with transplantation procedures Immunosuppression is a risk factor for NMSC. Patients receiving immunosuppressive therapy following solid organ transplantation and those receiving bone marrow transplants have an increased risk of skin cancer. In a small series of patients (n = 43) receiving nonmyeloablated haematopoietic cell transplants, 6 patients developed squamous cell carcinoma (n = 3), basal cell carcinoma (n = 2), or malignant melanoma (n = 2). In another study, the most frequently observed secondary malignancies among patients (n = 557) receiving allogeneic bone marrow transplants were NMSC. Out of 31 secondary malignancies, 5 were basal cell carcinoma and 4 were squamous cell carcinoma skin cancers.
Risk minimisation measures	Routine risk minimisation measures • Section 4.4 of SmPC mentioning warning of second primary malignancy and advice for cancer screening. • Listed as ADRs in section 4.8 of SmPC. • Advice to patients provided in product label Additional risk minimisation measures • HCP and patient educational material (HCP and patient brochures)

Table 11: Part VI.5- Important Identified Risk Related to Indication/Target Population:

For MCL (Mantle cell lymphoma) and FL (follicular lymphoma): TFR (tumour Flare Reaction)

Evidence for linking the risk to the medicine	Based on clinical trial data, lenalidomide may increase the risk of TFR in patients with CLL and other lymphomas.
Risk factors and risk groups	Tumour flare reaction has been associated with greater tumour burden in patients with CLL.
Risk minimisation measures	Routine risk minimisation measures • Section 4.2 and 4.4 of SmPC • Listed as an ADR in Section 4.8 of SmPC. Additional risk minimisation measures • HCP educational material (HCP brochure)

Table 12: Part VI.6-Cardiac Failure

Evidence for linking the risk to the medicine	Based on clinical trial data, a higher incidence of cardiac failure has been observed; the reason for this is not clear.
Risk factors and risk groups	No particular risk groups or risk factors have been identified for lenalidomide. In MM no differences in frequency, severity, serious outcomes and apparent risk level of cardiac failure AEs have been observed. Cardiac symptoms in patients with MDS are often due to anaemia and may be due to iron overload and side effects of therapy. In a study of 840 MDS patients, Della Porta reported that heart failure (28% versus 18%, p = 0.001) and cardiac death (69% versus 55%, p = 0.03) were significantly more frequent in transfusion-dependent patients. In a Cox analysis with time-dependent covariates, transfusion-dependent patients showed an increased risk of nonleukemic death (HR = 2.12; p ≤ 0.001), heart failure (HR = 1.34; p = 0.03), and cardiac death (HR = 2.99; p = 0.01). The development of secondary iron overload significantly affected the risk of non-leukemic death and OS (HR = 1.25 and 1.16, respectively; p < 0.001), and this effect was maintained after adjusting for transfusion burden. Iron overload specifically increased the risk of developing heart failure (HR = 1.17, p < 0.001). General risk factors for congestive heart failure include increasing age, previous heart disease, diabetes, hypertension, amyloidosis and previous anthracycline based chemotherapy treatment. Standard risk factors for atrial fibrillation include advancing age, European ancestry, body size (greater height and body mass index), electrocardiography features (left ventricular hypertrophy, left atrial enlargement), diabetes, systolic blood pressure and presence of cardiovascular disease (ie, CHD, heart failure, valvular heart disease). Other factors include clinical and subclinical hyperthyroidism, chronic kidney disease, and heavy alcohol consumption. Familial aggregation studies have identified a role for genetic factors, although such factors probably account for a small proportion of cases. In a case-control study of 385 eligible cases of new-onset atrial fibrillation embedded within the Rotterdam study, the risk of new-onset atrial fibrillation was significantly higher for persons who received a corticosteroid prescription within 1 month before the atrial fibrillation index date. Only high-dose corticosteroid use was associated with increased risk (OR = 6.07; 95% CI: 3.90-9.42). The association of atrial fibrillation was independent of indication for use. Risks were increased not only in patients with asthma or chronic obstructive pulmonary disease, but also in patients with rheumatic, allergic, or malignant haematologic diseases.
Risk minimisation measures	Routine risk minimisation measures • Listed as ADRs in section 4.8 of SmPC. Additional risk minimisation measures • Not applicable as there are no additional risk minimisation measures for this safety concern

Table 13: Part VI.7- Cardiac Arrhythmias

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. Based on clinical trial data, a higher incidence of cardiac arrhythmias was observed in the lenalidomide arm.
Risk factors and risk groups	No particular risk groups or risk factors have been identified for lenalidomide. In MM no differences in frequency, severity, serious outcomes and apparent risk level of cardiac failure AEs have been observed. Cardiac symptoms in patients with MDS are often due to anaemia and may be due to iron overload and side effects of therapy. In a study of 840 MDS patients, Della Porta reported that heart failure (28% versus 18%, p = 0.001) and cardiac death (69% versus 55%, p = 0.03) were significantly more frequent in transfusion-dependent patients. In a Cox analysis with time-dependent covariates, transfusion-dependent patients showed an increased risk of nonleukemic death (HR = 2.12; p ≤ 0.001), heart failure (HR = 1.34; p = 0.03), and cardiac death (HR = 2.99; p = 0.01). The development of secondary iron overload significantly affected the risk of non-leukemic death and OS (HR = 1.25 and 1.16, respectively; p < 0.001), and this effect was maintained after adjusting for transfusion burden. Iron overload specifically increased the risk of developing heart failure (HR = 1.17, p < 0.001). General risk factors for congestive heart failure include increasing age, previous heart disease, diabetes, hypertension, amyloidosis and previous anthracycline based chemotherapy treatment. Standard risk factors for atrial fibrillation include advancing age, European ancestry, body size (greater height and body mass index), electrocardiography features (left ventricular hypertrophy, left atrial enlargement), diabetes, systolic blood pressure and presence of cardiovascular disease (ie, CHD, heart failure, valvular heart disease). Other factors include clinical and subclinical hyperthyroidism, chronic kidney disease, and heavy alcohol consumption. Familial aggregation studies have identified a role for genetic factors, although such factors probably account for a small proportion of cases. In a case-control study of 385 eligible cases of new-onset atrial fibrillation embedded within the Rotterdam study, the risk of new-onset atrial fibrillation was significantly higher for persons who received a corticosteroid prescription within 1 month before the atrial fibrillation index date. Only high-dose corticosteroid use was associated with increased risk (OR = 6.07; 95% CI: 3.90-9.42). The association of atrial fibrillation was independent of indication for use. Risks were increased not only in patients with asthma or chronic obstructive pulmonary disease, but also in patients with rheumatic, allergic, or malignant haematologic diseases.
Risk minimisation measures	Routine risk minimisation measures • Listed as ADRs in section 4.8 of SmPC. • Listed in PL. Additional risk minimisation measures • Not applicable as there are no additional risk minimisation measures for this safety concern

Table 14: Part VI.8- Ischaemic Heart disease (including Myocardial Infarction)

Evidence for linking the risk to the medicine	In clinical trials, ischaemic heart disease has been reported in patients treated with lenalidomide. Myocardial infarction occurs relatively often in individuals of the older age groups that most often develop the target indication of MM, MDS, MCL and FL.
Risk factors and risk groups	Risk factors for 10-year coronary risk based upon the Framingham Heart Study include elevated blood pressure, elevated cholesterol, high-density lipoprotein c, presence of diabetes and cigarette smoking. These factors are in addition to well-known relationships between coronary risk and age and gender. In Europe, smoking remains a major public health issue and about 20% of death from CVD in men and about 3% of deaths from CVD in women are due to smoking. Levels of obesity are high across Europe in both adults and children and participation in physical activity is low. The prevalence of diabetes in Europe is high and has increased rapidly over the last ten years, increasing by more than 50% in many countries.
Risk minimisation measures	Routine risk minimisation measures • The association between ischaemic heart disease and lenalidomide is unknown. • Myocardial infarction is included in sections 4.4 and 4.8 of the SmPC. Additional risk minimisation measures • Not applicable as there are no additional risk minimisation measures for this safety concern

Table 15: Part VI.8-Off-label Use

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

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation for Lenalidomide Mylan.

II.C.2 Other Studies in Post-Authorisation Development Plan

Monitoring of Pregnancy Prevention Programme Implementation

Purpose of the study: Monitoring implementation of the Pregnancy Prevention Programme.

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

IIR/IPR	Follow up form title
Teratogenicity	• Event-specific questionnaire for HCP – Pregnancy background • Event-specific questionnaire for HCP – Pregnancy follow up • Event-specific questionnaire for HCP – Pregnancy Outcome • Event-specific questionnaire for HCP – Infant follow up
Serious infection due to neutropenia	Neutropenia
Second primary malignancies (SPM)	Second primary malignancies
For MCL (Mantle cell lymphoma) and FL (follicular lymphoma): TFR	TFR
Cardiac failure	Cardiac failure
Cardiac arrhythmias	Cardiac arrythmias and ECG changes
Ischaemic heart disease (including myocardial infarction)	Myocardial infarction
Off-label use	Off-label use

VIATRIS

TARGETED FOLLOW UP FORM FOR HCP — PREGNANCY BACKGROUND (PATIENT OR PARTNER OF PATIENT)

Viatris Case No.:

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:	
Indication for use:			
Cytogenetic abnormalities: □ No □ Yes If yes, specify:			
Current Pregnancy			
Date of last Menstrual period:		Estimated Delivery date:	

Pregnancy Test	Reference range	Date			
Urine qualitative					
Serum qualitative					
Prenatal Test:					
	Date	Result			
Ultrasound					
Ultrasound					

VIATRIS

TARGETED FOLLOW UP FORM FOR HCP — PREGNANCY BACKGROUND (PATIENT OR PARTNER OF PATIENT)

Viatris Case No.:

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 □ Other Specify:		
Did birth defect occur in any previous pregnancy: □ No □ Yes □ Unknown If yes, specify:		
Did a still birth or miscarriage occur in any previous pregnancy □ No □ Yes □ Unknown 1) If yes, in what week of pregnancy did the stillbirth of miscarriage occur? ____week 2)Was there any birth defect noted? □ No □ Yes If Yes, specify:		

Relevant medical history
□ No □ Yes If Yes, specify:

	Date of diagnosis		Date of diagnosis
Cancer □ No □ Yes, If Yes, Specify			

Social history			
Alcohol □ No □ Yes, If Yes, amount/Units consumed per day:			
Tobacco □ No □ Yes	IV or recreational drug use □ No □ Yes, specify:		
Family history: Congenital abnormalities □ No □ Yes If Yes, specify:			
Is there 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 dietary supplements) During pregnancy			
Medication/Treatment	Start Date	Stop Date/Ongoing	Indication

VIATRIS

TARGETED FOLLOW UP FORM FOR HCP — PREGNANCY BACKGROUND (PATIENT OR PARTNER OF PATIENT)
Viatris Case No.:

Adverse event(s) during pregnancy

Event(s)	**Serious**		**Serious Criteria[1]**	**Start Date**	**Stop Date/Ongoing**	**Causal relationship to lenalidomide**		
	No	Yes				Yes	No	If No, what medications, disease states etc, Played a role of the event?

[1] Serious Criteria: 1) Death 2) life-threatening 3) required inpatient hospitalisation or prolongation of existing hospitalisation 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 suing while on lenalidomide 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

VIATRIS

TARGETED FOLLOW UP FORM FOR HCP — PREGNANCY BACKGROUND (PATIENT OR PARTNER OF PATIENT)

Viatris Case No.:

2. Was your patient or their partner without contraception for even 1 day at any time during use of lenalidomide?

□ No, please proceed to Question 5
□ Yes, please answer Questions 3-6

3. If applicable per Question 2, how often did your partner 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 use
□ other, specify

5. Please ask your patient if they received lenalidomide Patient educational material 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 lenalidomide Patient educational material 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 lenalidomide Patient educational material 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 pomalidomide use came from

□ physician who prescribed pomalidomide
□ Patient educational material or patient leaflet
□ other, specify:

6. Please ask your patient if they felt like they and their partner had a good understanding of the risk of pregnancy during lenalidomide use

□ No

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TARGETED FOLLOW UP FORM FOR HCP — PREGNANCY BACKGROUND (PATIENT OR PARTNER OF PATIENT)
Viatris Case No.:

□ Yes □ don't know

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Signature of person completing this form: _____ **Date:** _____

Please be aware that information provided to Viatris relating to you, may be used to comply with applicable laws and regulations. Viatris processes your personal or sensitive data in accordance with applicable data protection laws and the Viatris Privacy Statement, available to you either on https://www.viatris.com/en/viatris-privacy-notice or upon request.

Additional Information: _____

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VIATRIS

TARGETED FOLLOW UP FORM FOR HCP – PREGNANCY FOLLOW UP
(Patient or Partner of Patient)

Viatris Case No.:

Telephone:
Fax:
Email:

Date:	Period covered: _____to_____ Date 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	

	Date	Result
Ultrasound		
Ultrasound		
Ultrasound		
Amniocentesis		
Maternal Serum AFP		
Other tests, specify:		

Medications/Treatments (Including herbal, alternative and over the counter medicines dietary supplements) During pregnancy

Drug	Start Date	Stop Date/Ongoing	Indication

Adverse event(s) during pregnancy

Event(s)	**Serious**		**Serious Criteria[1]**	**Start Date**	**Stop Date**	**Causal relationship to lenalidomide**		
	No	Yes				Yes	No	If No, what medications, disease

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TARGETED FOLLOW UP FORM FOR HCP – PREGNANCY FOLLOW UP (Patient or Partner of Patient)
Viatris Case No.:

								states etc, Played a role of the event?

[1] Serious Criteria: 1) Death 2) life-threatening 3) required inpatient hospitalisation or prolongation of existing hospitalisation 4) a persistent or significant disability/incapacity 5) a congenital anomaly /birth defect 6) medically significant.

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Signature of person completing this form:_____ **Date:** _____

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Additional Information: _____

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VIATRIS

TARGETED FOLLOW UP FORM FOR HCP — PREGNANCY OUTCOME
(Patient or Partner of Patient)

Viatris Case No.:

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 □ African-American □ Asian □ Other, Specify:
Partner of Patient Information □ Not applicable		
Date of Birth	Ethnicity: □ White □ African-American □ Asian □ Other, Specify:	
Pregnancy type □ Singleton □ Twins □ Triplet □ Other, specify:		
Pregnancy outcome		
Date of delivery:		Gestation age at delivery:

Delivery details:	No	Yes	
Normal	☐	☐	
C-Section	☐	☐	
Induced	☐	☐	
Assisted (e.g. forceps)	☐	☐	
Ectopic pregnancy	☐	☐	
Elective termination	☐	☐	Date:
Spontaneous abortion (≤ 20 weeks)	☐	☐	Weeks from LMP:
Fetal death/Still birth (> 20 weeks)	☐	☐	
Were the product of conception examined?	☐	☐	If yes, was fetus normal? ☐ Yes ☐ No ☐ Unknown If no, describe:

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TARGETED FOLLOW UP FORM FOR HCP — PREGNANCY OUTCOME
(Patient or Partner of Patient)

Viatris Case No.:

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 and neonatal status			
	No	Yes	
Live normal infant	☐	☐	
Fetal distress	☐	☐	
Intra-uterine growth retardation	☐	☐	
Neonatal complications*	☐	☐	If yes, specify:
Birth defect noted?	☐	☐	If yes, specify:

* please provide a brief summary of the management of the complications

Sex: ☐ Male ☐ Female
Birth weight: _____lbs_____oz **or**_____ kg
Length: _____Inches **or**_____ cm

Apgar Score:	Unknown:	1min:	5mins:	10mins:

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Additional Information: _____

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VIATRIS

TARGETED FOLLOW UP FORM FOR HCP – INFANT FOLLOW UP

Viatris Case No.:

Telephone:
Fax:
Email:

Date of Assessment:

Name of patient on lenalidomide:

Name of Infant (If known):

Age of infant (in months):

Weight: _____lbs_____oz **or**_____ kg

Length: _____Inches **or**_____ cm

Please provide information for the period from _____(Date) to _____ (Date)

Birth defects/Anomalies
New birth defects or anomalies diagnosed since the previous report?_____

☐ Yes □No

If **yes**, please list the birth defects/anomalies below:

Birth Defect/Anomaly	**Was the birth defect/anomaly attributed to lenalidomide?** (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)

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TARGETED FOLLOW UP FORM FOR HCP – INFANT FOLLOW UP
Viatris Case No.:

Developmental Assessment: _____

Is the child developing normal 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 illness, Hospitalisation, Drug therapies:

Infant illness	Hospitalisation	Drug therapies
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	

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Signature of person completing this form: _____ **Date:** _____

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Additional Information: _____

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VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case No.:

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-MMM-YYYY)			
Stop date (DD-MMM- 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)

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case No.:

Adverse Event (AE) Description: Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

	Adverse Event #1	Adverse Event #2	Adverse Event #3	Adverse Event #4
Add Diagnosis Here				
Start Date (DD/MMM/YYYY)				
Stop Date (DD/MMM/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)				

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TARGETED FOLLOW UP FORM
Viatris Case No.:

Please summarize course of reported events including signs and symptoms in chronological order_____
_____
_____

On or about (DDMMYYYY), your patient was reported to have experienced neutropenia. Please provide the following lab values, onset of the event (worst), and recovery:

Date	Test	Pre-treatment value	AE onset value	AE resolution value	Normal low	Normal high
	WBC					
	NAC					

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-MMM-YYYY	Stop date DD-MMM-YYYY

Other Etiological Factors: ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical and/or drug history (please specify), including start date or duration:

_____

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case No.:

_____

_____

☐ Family history (please specify):

☐ Drug/alcohol/tobacco abuse:

☐ Other (please specify):

Additional questions:

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

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

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

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

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

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

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

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TARGETED FOLLOW UP FORM
Viatris Case No.:

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

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

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Signature of person completing this form: _____ **Date:** _____

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Additional Information: _____

_____

_____

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case No.:

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-MMM-YYYY)			
Stop date (DD-MMM- 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.

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Viatris Case No.:

	Adverse Event #1	Adverse Event #2	Adverse Event #3	Adverse Event #4
Add Diagnosis Here				
Start Date (DD/MMM/YYYY)				
Stop Date (DD/MMM/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

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case No.:

_____

_____

—

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	Start date DD-MMM-YYYY	Stop date DD-MMM-YYYY

Other Etiological Factors: ☐ Yes (please complete below) ☐ None ☐ Unknown

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TARGETED FOLLOW UP FORM
Viatris Case No.:

☐ Relevant medical history (including history of malignancies) and/or drug history (please specify), including start date or duration:_____

_____

☐ Family history (please specify), including history of malignancies with estimated dates:__

☐ Drug/alcohol/tobacco abuse:__

☐ Other (please specify):__

Additional questions:

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

Core questions for follow-ups of SPM:

1. Dates of underlying disease's diagnosis
2. Date of diagnosis of SPM (*specify malignancy or diagnosis, if known*). Please provide 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 with exact stage. 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 of family history of thyroid and/or autoimmune disease – 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 iodine deficient area
- History of radiation exposure

Breast cancer:

- Receptor status of the tumour – ER, PR, Her2/neu

- Age at onset of menses and age at menopause
- Number of pregnancies and age at 1st 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 at 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, 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
- Alcohol use
- Hepatitis B, C
- Hemochromatosis
- Ingestion of food contaminated with fungal aflatoxins (in subtropical regions)

Pancreatic cancer:

- Smoking
- Obesity
- Diet (red meat)
- History of chronic pancreatitis or long-standing diabetes mellitus (primarily in women)
- Inherited predisposition hereditary pancreatitis, familial adenomatous polyposis

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 analgesic taken in large amounts
- History of renal transplantation
- Exposure to radiopaque dyes, asbestos, cadmium and other leather tanning and petroleum products
- Inherited VHL disease (von Hippel-Lindau disease), adult polycystic kidney disease, Tuberous sclerosis

Bladder cancer:

- Smoking 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 metals
- 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 infusion 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 smoking and alcohol use
- 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 tumours (gliomas and meningiomas):

- Exposure to radiation
- Exposure to vinyl chloride, pesticides
- Immune system disorders
- Hormone replacement therapy

Larynx cancer:

- History of smoking history and alcohol use
- Exposure to asbestos
- 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 HPV
- Smoking Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting

Mouth and Oropharyngeal cancer:

- History of alcohol use/smoking
- History of poor oral hygiene
- Chronic mucosal/gum irritation / ill-fitting dentures
- Betel-Nut Chewing (Indian populations)
- History of syphilis or viral infections
- Impaired immunity -AIDS, transplant with anti-rejection drugs
- Precancerous moth 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, 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 melanocytes or dysplastic nevus syndrome

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Signature of person completing this form: _____ **Date:** _____

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Additional Information: _____

_____

_____

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case No.:

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-MMM-YYYY)			
Stop date (DD-MMM- 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)

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case No.:

Adverse Event (AE) Description: Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

	Adverse Event #1	Adverse Event #2	Adverse Event #3	Adverse Event #4
Add Diagnosis Here				
Start Date (DD/MMM/YYYY)				
Stop Date (DD/MMM/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:

_____

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case No.:

_____

_____

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					
	Lymphocytes					
	Hb					
	Platelets					
	LDH					
	Creatinine					
	Calcium					
	Phosphorus					
	Albumin					
	CRP					

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 Include at least other chemotherapies, higher dose chemotherapy, treatment with immuno-modulator, hormonotherapy.

Medication Name	Daily dose and regimen	Route of administration	Indication	Start date DD-MMM-YYYY	Stop date DD-MMM-YYYY

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case No.:

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:

Provide lenalidomide product dosing with therapy start date, all doses prior to the tumor flare reaction

Please confirm the chemotherapy indication

Tumour burden (to specify) or disease stage as baseline and at the time of event

Details of associated symptoms: Fever (please provide temperature value); pain (please specify); rash (details on zones); tender lymph nodes/swelling (specify location); tender liver or spleen, elevated WBC counts, other (to specify)

Any complication (to specify)

Imagery results (CT scan/MRI) at baseline and at the time of the event

VIATRIS

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Infections work-up (serologies, cultures – blood/urine/sputum/stools), chest X-ray

Does this patient have a history of previous tumour flare?

☐Yes (if yes, please describe)
☐No
☐Unknown

Provide the action taken with lenalidomide drug:

☐None	
☐Permanently discontinued	Stop date:
☐Temporary interrupted	Stop date:
☐Dose reduced	Date and new dose:
☐Dose increased	Date and new dose:

Did the event abate after discontinuing lenalidomide?

☐Yes
☐No

Was lenalidomide product re-introduced?

☐Yes, if yes, please provide restart date and dosing:
☐No

Provide action taken with concomitant chemotherapy (to specify):

☐None	
☐Permanently discontinued	Stop date:
☐Temporary interrupted	Stop date:
☐Dose reduced	Date and new dose:
☐Dose increased	Date and new dose:

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case No.:

Did the event abate after discontinuing concomitant chemotherapy?

☐Yes
☐No

Was concomitant chemotherapy re-introduced?

☐Yes, if yes, please provide restart date and dosing:
☐No

Treatment of tumour flare (details):

_____

_____

Response to treatment:

_____

_____

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Signature of person completing this form: _____ **Date:** _____

Please be aware that information provided to Viatris relating to you, may be used to comply with applicable laws and regulations. Viatris processes your personal or sensitive data in accordance with applicable data protection laws and the Viatris Privacy Statement, available to you either on https://www.viatris.com/en/viatris-privacy-notice or upon request.

Additional Information: _____

_____

_____

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case No.:

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-MMM-YYYY)			
Stop date (DD-MMM- 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)

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case No.:

Adverse Event (AE) Description: Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

	Adverse Event #1	Adverse Event #2	Adverse Event #3	Adverse Event #4
Add Diagnosis Here				
Start Date (DD/MMM/YYYY)				
Stop Date (DD/MMM/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:

_____

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case No.:

_____

_____

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-MMM-YYYY	Stop date DD-MMM-YYYY

Other Etiological Factors: □ Yes (please complete below) □ None □ Unknown

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case No.:

□ 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) If the cardiac failure occurred prior to therapy, would you consider it an exacerbation? □Yes □ No
   b) Please provide the date the exacerbation was diagnosed _____

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 and angiogram, CT scan, MRI and ejection fraction

Did the patient receive any recent blood transfusion or IV fusion? □Yes □ No
If yes, please specify what was transfused and provide the amount transfused with dates

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case No.:

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? other chemotherapy (previous and ongoing) etc?

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.

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

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

What treatments /interventions were provided to the patient for the cardiac failure?

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Signature of person completing this form: _____ Date: _____

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Additional Information: _____

_____

_____

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case No.:

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-MMM-YYYY)			
Stop date (DD-MMM- 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)

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case No.:

Adverse Event (AE) Description: Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

	Adverse Event #1	Adverse Event #2	Adverse Event #3	Adverse Event #4
Add Diagnosis Here				
Start Date (DD/MMM/YYYY)				
Stop Date (DD/MMM/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)				

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case 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):

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TARGETED FOLLOW UP FORM
Viatris Case No.:

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	Start date DD-MMM-YYYY	Stop date DD-MMM-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), including history of malignancies with estimated dates:__
☐ Drug/alcohol/tobacco abuse:__
☐ Other (please specify):__

Additional questions:

Please provide brief description of the cardiac arrhythmia, or EKG 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 start)

Start date Stop date

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

Does this patient have a relevant cardiac risk factors (e.g., hypertension, hyperlipidemia, hypercholesteremia, diabetes, obesity, sepsis, smoking, renal disease, cardiorespiratory problems)? If yes, please specify in box below. If no, please start

TARGETED FOLLOW UP FORM
Viatris Case No.:

Medical history (Diagnosis)	Onset date / Duration

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

Test	Baseline		Event Onset/Worst		Recovery/Latest	
	Date	Results	Date	Results	Date	Results
EKG findings						
Echocardiogram						
Chest X-ray						
Holter, Stress test						

Please describe specific treatments and interventions of the arrhythmia

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Signature of person completing this form: _____ _____ Date: _____

Please be aware that information provided to Viatris relating to you, may be used to comply with applicable laws and regulations. Viatris processes your personal or sensitive data in accordance with applicable data protection laws and the Viatris Privacy Statement, available to you either on https://www.viatris.com/en/viatris-privacy-notice or upon request.

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TARGETED FOLLOW UP FORM
Viatris Case No.:

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-MMM-YYYY)			
Stop date (DD-MMM- 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)

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case No.:

Adverse Event (AE) Description: Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

	Adverse Event #1	Adverse Event #2	Adverse Event #3	Adverse Event #4
Add Diagnosis Here				
Start Date (DD/MMM/YYYY)				
Stop Date (DD/MMM/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)				

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case 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					
	Magnesium					
	Calcium					

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-MMM-YYYY	Stop date DD-MMM-YYYY

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case No.:

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, hypercholesteremia, obesity, hypertension, COPD, renal disease, diabetes, sepsis, substance abuse, sedentary of life, immobility, dehydration, etc)

Please provide the following diagnostic results including the baseline and the most recent EKG, echocardiogram, stress test, and cardiac catheterisation, if available

Please provide the treatment and intervention that were administered due to the myocardial infarction

Please provide concurrent events/circumstances surroundings the MI

TARGETED FOLLOW UP FORM
Viatris Case No.:

Did the patient have a history of chest pain

Did the patient have a history of thromboembolic events? If yes, please specify type

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Signature of person completing this form: _____ **Date:** _____

Please be aware that information provided to Viatris relating to you, may be used to comply with applicable laws and regulations. Viatris processes your personal or sensitive data in accordance with applicable data protection laws and the Viatris Privacy Statement, available to you either on https://www.viatris.com/en/viatris-privacy-notice or upon request.

TARGETED FOLLOW UP FORM
Viatris Case No.:

You recently reported off-label use in a patient. We would like to ask you to complete this questionnaire. The information you provide will help us monitor and mitigate safety concerns associated with the use of Lenalidomide.

Answering this questionnaire is entirely voluntary and should not take more than 10 minutes of your time. Please complete the form and send it back to:

<mail>@viatris.com

or

<fax> (+ xxx)

1. Patients Details:

Patient's Initials	
Age/Date of birth	
Gender	
Weight	
Height	

2. Product Details:

Tradename	
Strength	
Batch number	
Expiry date	
Route of administration	
Dose	
Dose frequency	
Start date	
Stop date	
Onset date for event	

3. Type of Off-label use:

☐ Different indication

☐ Different route/method of administration

☐ Different dosing

☐ Different dosing frequency

Viatris use only

TARGETED FOLLOW UP FORM
Viatris Case No.:

☐ Different target group (pregnancy/lactation/paediatrics/elderly/renal impairment/hepatic impairment-please select as applicable)

☐ Other

If 'Other', please specify: _____

_____

a) Details of Off-label use:

Name :

Licence Number :

Dose :

Dose Frequency :

Route of administration:

Off-label use in the context of:

☐ acute myelogenous leukaemia

☐ unspecified leukaemia

☐ peripheral blood stem cell apheresis/harvest

☐ myelodysplastic syndrome

☐ idiopathic neutropenia/agranulocytosis

☐ Other

If 'Other', please specify: _____

_____

b) Description of Adverse Event(s) associated with Off-label use:

_____

_____

_____

4. Outcome of Off-label use:

☐ Recovered/resolved

☐ Recovering/resolving

☐ Unknown

☐ Not recovered/resolved

☐ Fatal

☐ Other

If other, please specify:

_____

_____

TARGETED FOLLOW UP FORM
Viatris Case No.:

5. Reporter's Details:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name: Sign:

Occupation: Date:

Please be aware that information provided to Viatris relating to you, may be used to comply with applicable laws and regulations. Viatris processes your personal or sensitive data in accordance with applicable data protection laws and the Viatris Privacy Statement, available to you either on https://www.viatris.com/en/viatris-privacy-notice or upon request.

Additional Information:

_____

_____

_____

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (If Applicable)

Additional risk minimisation measures

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 Mylan are provided with an Educational Healthcare Professional's Kit containing the following:
- Educational healthcare professional's brochure
- Educational brochures for patients
- Patient card
- Risk awareness forms
- Information on where to find the 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

Educational Healthcare Professional's Kit

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 Mylan for healthcare professionals and caregivers
- Obligations of the health care professional who intend to prescribe or dispense Lenalidomide Mylan
    - 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 Mylan
    - 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 tumour flare reaction in MCL and FL patients

  - Description of the risk of progression to AML in MDS patients, including incidence rates from clinical trials
  - Description of risk of SPM
  - Local country specific arrangements for a prescription for Lenalidomide Mylan 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 Mylan

- 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 Mylan 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 contraceptions (even if the man has had a vasectomy)
    - During Lenalidomide Mylan 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 Mylan treatment
  - That i f his partner becomes pregnant whilst he is taking Lenalidomide Mylan or shortly after he has stopped taking Lenalidomide Mylan he should inform his treating doctor immediately
- Requirements in the event of pregnancy
  - Instructions to stop Lenalidomide Mylan 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 Mylan for patients, caregivers and family members
- National or other applicable specific arrangements for a prescription for Lenalidomide Mylan to be dispensed
- That the patient must not give Lenalidomide Mylan 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 Mylan 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:

<u>Brochure for women patients with childbearing potential</u>

- The need to avoid foetal exposure
- Description of the PPP
- The need 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 during dose interruptions), at least every 4 weeks except in case of confirmed tubal sterilisation
    - After finishing treatment
- The need to stop Lenalidomide Mylan immediately upon suspicion of pregnancy
- The need to contact their doctor immediately upon suspicion of pregnancy

<u>Brochure for male patients</u>

- The need to avoid foetal exposure
- The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraceptions (even if the man has had vasectomy)
    - During Lenalidomide Mylan 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 7 days following discontinuation of Lenalidomide Mylan treatment

<u>Patient Card or equivalent tool</u>

The patient card shall contain the following elements:

- Verification that appropriate counselling has taken place
- Documentation of childbearing potential status
- Checkbox (or similar) which physician ticks to confirm the 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 4 weeks before starting treatment, throughout the entire duration of treatment, and at least 4 weeks 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 Mylan
        - the physician prescribing Lenalidomide Mylan 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 Mylan 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 Mylan
    - 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 Mylan
    - 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 Mylan