EU/UK Risk Management Plan
for
Lenalidomide Accord 2.5 mg hard capsules
Lenalidomide Accord 5 mg hard capsules
Lenalidomide Accord 7.5 mg hard capsules
Lenalidomide Accord 10 mg hard capsules
Lenalidomide Accord 15 mg hard capsules
Lenalidomide Accord 20 mg hard capsules
Lenalidomide Accord 25 mg hard capsules
(Lenalidomide)

RMP version to be assessed as part of this application:

RMP Version number	2.0
Data lock point for this RMP	26-Oct-2023
Date of final sign off	20-Jan-2024

Rationale for submitting an updated RMP: This is RMP has been updated in-line with EPAR Risk Management Plan of Revlimid (lenalidomide) published on 20-Oct-2023.

Summary of significant changes in this RMP: Significant changes have been made in following sections of RMP: Part I, Part II, Part III, Part V, Part VI and Part VII (Annex 6 and Annex 8).

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

Version number	Approved with procedure	Date of approval (opinion date)
1.7	EMEA/H/C/004857/IB/0015/G	10-May-2021

QPPV name: Agata Gesiewicz

QPPV signature: [redacted]

[redacted]

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Part I: Product(s) Overview

Table 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	Accord Healthcare SLU, Spain Accord Healthcare Limited
Medicinal products to which this RMP refers	07
Invented name(s) in the European Economic Area (EEA)/United Kingdom (UK)	Lenalidomide Accord 2.5 mg hard capsules Lenalidomide Accord 5 mg hard capsules Lenalidomide Accord 7.5 mg hard capsules Lenalidomide Accord 10 mg hard capsules Lenalidomide Accord 15 mg hard capsules Lenalidomide Accord 20 mg hard capsules Lenalidomide Accord 25 mg hard capsules
Marketing authorisation procedure	Centralised procedure (EMEA/H/C/0004857) UK National (PLGB 20075 1291-1297)
Brief description of the product	Chemical class: Other immunosuppressants
	Summary of mode of action: Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1). In haematopoietic cells, lenalidomide binds to cereblon recruits substrate proteins Aiolos and Ikaros lymphoid transcriptional

[redacted]

	factors, leading to their ubiquitination and subsequent degradation resulting in direct cytotoxic and immunomodulatory effects. Specifically, lenalidomide inhibits proliferation and enhances apoptosis of certain haematopoietic tumour cells (including MM plasma tumour cells and follicular lymphoma tumour cells), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK, T and NK T cells. The combination of lenalidomide and rituximab increases ADCC and direct tumor apoptosis in follicular lymphoma cells. The lenalidomide mechanism of action also includes additional activities such as anti-angiogenic and pro-erythropoietic properties. Lenalidomide inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL 6) by monocytes.
	Important information about its composition Lenalidomide Accord 2.5 mg hard capsules Each hard capsule contains 2.5 mg of lenalidomide. *Excipient with known effect* Each hard capsule contains 36 mg of lactose. Lenalidomide Accord 5 mg hard capsules Each hard capsule contains 5 mg of lenalidomide. *Excipient with known effect* Each hard capsule contains 33 mg of lactose. Lenalidomide Accord 7.5 mg hard capsules Each hard capsule contains 7.5 mg of lenalidomide. *Excipient with known effect*

	Each hard capsule contains 50 mg of lactose. Lenalidomide Accord 10 mg hard capsules Each hard capsule contains 10 mg of lenalidomide. *Excipient with known effect* Each hard capsule contains 67mg of lactose. Lenalidomide Accord 15 mg hard capsules Each hard capsule contains 15 mg of lenalidomide. *Excipient with known effect* Each hard capsule contains 100 mg of lactose. Lenalidomide Accord 20 mg hard capsules Each hard capsule contains 20 mg of lenalidomide. *Excipient with known effect* Each hard capsule contains 134 mg of lactose Lenalidomide Accord 25 mg hard capsules Each hard capsule contains 25 mg of lenalidomide. *Excipient with known effect* Each hard capsule contains 167 mg of lactose.
Hyperlink to the Product Information	Please refer Module 1.3.1 for SmPC and PIL
Indication(s) in the EEA/UK	*Current* Multiple myeloma Lenalidomide Accord as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.

[redacted]

	Lenalidomide Accord 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 Accord in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy. <u>Myelodysplastic syndromes</u> Lenalidomide Accord 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. <u>Mantle cell lymphoma</u> Lenalidomide Accord as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma. <u>Follicular lymphoma</u> Lenalidomide Accord 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/UK	*<u>Current</u>* **<u>Posology</u>** *<u>Newly diagnosed multiple myeloma (NDMM)</u>* • <u>Lenalidomide maintenance in patients who have undergone autologous stem cell transplantation (ASCT)</u>

[redacted]

	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 • 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. The recommended dose of dexamethasone is 40 mg orally once daily on days 1, 8, 15 and 22 of repeated 28-day cycles. Patients may continue lenalidomide and dexamethasone therapy until disease progression or intolerance. • Lenalidomide in combination with bortezomib and dexamethasone followed by lenalidomide and dexamethasone until disease progression in patients who are not eligible for transplant *Initial treatment:* Lenalidomide in combination with bortezomib and dexamethasone

	Lenalidomide in combination with bortezomib and dexamethasone must not be started if the ANC is < 1.0 x 10^9/L, and/or platelet counts are < 50 x 10^9/L. The recommended starting dose is lenalidomide 25 mg orally once daily days 1-14 of each 21-day cycle in combination with bortezomib and dexamethasone. Bortezomib should be administered via subcutaneous injection (1.3 mg/m^2 body surface area) twice weekly on days 1, 4, 8 and 11 of each 21-day. Up to eight 21-day treatment cycles (24 weeks of initial treatment) are recommended. *Continued treatment:* Lenalidomide in combination with dexamethasone until progression Continue lenalidomide 25 mg orally once daily on days 1-21 of repeated 28-day cycles in combination with dexamethasone. Treatment should be continued until disease progression or unacceptable toxicity. • <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

[redacted]

	orally once daily on days 1 to 21 of repeated 28-day cycles given until disease progression. *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. Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient. *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.

[redacted]

	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.
Pharmaceutical form(s) and strengths	*Current* Hard capsule 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20mg and 25 mg
Is the product subject to additional monitoring in the EU/UK?	No

[redacted]

Part II: Safety specification

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

Not applicable

Module SII - Non-clinical part of the safety specification

Not applicable

Module SIII - Clinical trial exposure

Not applicable

Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Not applicable

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Not applicable

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Not applicable

Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable

Module SVI - Additional EU/UK requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable - there is no potential for misuse for illegal purposes.

Module SVII - Identified and potential risks

The safety concerns for this Risk Management Plan (RMP) have been considered as per European Public Assessment Report (Summary of the RMP) for Revlimid® (lenalidomide) published 20-Oct-2023 on EMA website. There is no change proposed by MAH in these safety concerns mentioned in Module SVIII of this RMP which is in-line with summary of safety concerns for reference product Revlimid® (lenalidomide).

Hence this section remains "Not applicable".

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

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

[redacted]

Module SVIII - Summary of the safety concerns

Table 2: Summary of safety concerns

Important identified risks	• Teratogenicity • Serious infection due to neutropenia • Second primary malignancies (SPM) • Tumor flare reaction (Follicular lymphoma and Mantle cell lymphoma indications)
Important potential risks	• Cardiac failure • Cardiac arrhythmias • Ischaemic heart disease (including myocardial infarction) • Off-label use
Missing information	• None

[redacted]

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file are sufficient for the mentioned safety concerns.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for following risks concerning use of Lenalidomide:

- Teratogenicity
- Serious infection due to neutropenia
- Second primary malignancies (SPM)
- Tumour flare reaction
- Cardiac arrhythmia and ECG changes
- Cardiac failure
- Myocardial infarction
- Acute myeloid leukaemia and myelodysplastic syndromes

Purpose: For collection and reporting of safety information while use of Lenalidomide Accord.

Targeted follow-up questionnaires and data collection forms are appended in Annex 4 of this RMP.

III.2 Additional pharmacovigilance activities

Pregnancy prevention programme (PPP) for Lenalidomide Accord shall be implemented as Category 3 study to investigate teratogenicity an important identified risk and to evaluate the effectiveness of PPP as risk minimisation activities as conditions of the marketing authorisation or specific obligation of for Lenalidomide Accord hard capsules (2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg). Study details are summarised below in Part III.3 of this RMP.

[redacted]

III.3 Summary Table of additional Pharmacovigilance activities

Study; **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones** (required by regulators)	**Due dates**
Short title: Pregnancy prevention programme for Lenalidomide Accord (Category 3 study) Status: Planned	Monitoring of implementation and the effectiveness of PPP	Teratogenicity	Routine PSURs in-line with DLP of latest EURD list	Data will be reviewed on an on-going basis as a part of signal detection and reported within PSURs with in-line with EURD list

Part IV: Plans for post-authorisation efficacy studies

Not applicable

[redacted]

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

V.1. Routine Risk Minimisation Measures

Table 3: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Teratogenicity	Routine risk communication: • SmPC Sections: 4.3, 4.6, 4.8 and 5.3 • PIL Section: 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk*: SmPC Section 4.4: This section highlights the potential teratogenic effects of lenalidomide. Stringent controls are required to ensure exposure of an unborn child to lenalidomide does not occur. These include: • Criteria for women of non-childbearing potential • Counseling • Contraception • Pregnancy testing • Precautions for men • Additional precautions • Reference to educational materials, prescribing and dispending restrictions Other routine risk minimisation measures beyond the Product Information:

Safety concern	**Routine risk minimisation activities**
Important Identified Risks	
	Pack size: The pack is based on a maximum 4-week supply of capsules to ensure that FCBP (Females of child bearing potential) are required to obtain a new monthly prescription with a medically supervised pregnancy test. Legal status: Prescription only status of the product.
Serious infection due to neutropenia	<u>Routine risk communication:</u> • SmPC Section: 4.8 • PIL Section: 2 <u>*Routine risk minimisation activities recommending specific clinical measures to address the risk*</u>: • SmPC Section 4.2: Dose reduction advice for neutropenia. • SmPC Section 4.4: Warning of neutropenia, and infection with or without neutropenia, and advice for monitoring patients, including blood testing for neutropenia; Advice that patients should report febrile episodes promptly; Advice that HBV status should be established before initiating treatment with lenaliomide and advice to exercise caution when lenalidomide is used in patients previously infected with HBV. In addition, advice that patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy.

[redacted]

Safety concern	**Routine risk minimisation activities**
Important Identified Risks	
	• PIL Section 2: Advice to the doctor to check if the patient has ever had hepatitis B infection prior to lenalidomide treatment. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only status of the product.
Second primary malignancies (SPM)	Routine risk communication: • SmPC Section: 4.8 • PIL Section: 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk*: • SmPC Section 4.4: This section highlights the risk of SPM, and advises standard cancer screening before and during lenalidomide use, with instigation of treatment as necessary. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only status of the product.
Tumour flare reaction (Follicular lymphoma and Mantle cell lymphoma indications)	Routine risk communication: • SmPC Section: 4.8 • PIL Section: 2

Safety concern	**Routine risk minimisation activities**
Important Identified Risks	
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.2: This section includes dose interruption advice for Tumour flare reaction. • SmPC Section 4.4: This section highlights the risk of TFR in lenalidomide-treated patients with CLL and other lymphomas, and warns that tumour flare may mimic disease progression. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only status of the product.
Important Potential Risks	
Cardiac failure	Routine risk communication: • SmPC Section: 4.8 • PIL Section: 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk*: None Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only status of the product.

[redacted]

Safety concern	**Routine risk minimisation activities**
Important Identified Risks	
Cardiac arrhythmias	Routine risk communication: • SmPC Section: 4.8 • PIL Section: 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk*: None Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only status of the product
Ischaemic heart disease (including myocardial infarction)	Routine risk communication: • SmPC Section: 4.8 • PIL Section: 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk*: • SmPC Section 4.4: This section highlights the possible occurrence of MI, and advises monitoring of patients with known risk factors. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only status of the product

[redacted]

Safety concern	**Routine risk minimisation activities**
Important Identified Risks	
Off-label use	Routine risk communication: • SmPC Section: 4.4 *Routine risk minimisation activities recommending specific clinical measures to address the risk*: None Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only status of the product

V.2. Additional Risk Minimisation Measures

Additional Risk Minimisation Measures have been proposed for following risks as per reference medicinal product Revlimid® (lenalidomide).

Teratogenicity, second primary malignancies (SPM) and tumor flare reaction (Follicular lymphoma and Mantle cell lymphoma indication).

Proposed additional risk minimisation measures are listed below and are detailed summarised in Annex 6.

Additional risk minimisation 1

Healthcare Professionals (HCP) Educational Materials (HCP Brochure)

Objectives:

To increase an awareness of healthcare professionals regarding risk of teratogenicity, second primary malignancies and tumor flare reaction (Follicular lymphoma and Mantle cell lymphoma indication) with use of lenalidomide.

[redacted]

Rationale for the additional risk minimisation activity:

To minimise the reporting frequency of ADR related with this risk by increasing an awareness of healthcare professionals.

Target audience and planned distribution path:

Physician and other healthcare professionals who may prescribe lenalidomide.

Post approval of this MA application. MAH may distribute 'Guide for Healthcare Professional' to above mentioned target audience as per national requirement.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Routine pharmacovigilance including analysis of ADR reports to assess compliance with SmPC recommendations will allow assessing and judging the success of the risk minimisation measures. Effectiveness of the educational material for HCP will be analysed by MAH as per the requirements for submission of periodic safety update reports (PSUR) for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Additional risk minimisation 2

Pregnancy Prevention Programme (PPP)

Objectives:

To increase an awareness of healthcare professionals regarding risk of teratogenicity with use of lenalidomide.

Rationale for the additional risk minimisation activity:

To minimise the reporting frequency of ADR related with teratogenicity risk by increasing an awareness of healthcare professionals.

Target audience and planned distribution path:

Physician, patients or care taker of patients and all other healthcare professionals (eg, pharmacist, nurse, dentist).

Post approval of this MA application. MAH may distribute 'Pregnancy Prevention Programme' to above mentioned target audience as per national requirement.

Plans to evaluate the effectiveness of the interventions and criteria for success:

[redacted]

The terms of the Lenalidomide Accord Marketing Authorisation require Accord Healthcare Limited to assess the effectiveness of the Pregnancy Prevention Programme in order to ensure that all reasonable steps are being taken to reduce the risk of pregnancy in patients treated with Lenalidomide Accord. Pregnancy prevention programme for Lenalidomide Accord shall be implemented as Category 3 study. Study details are summarised in Part III.3 of this RMP.

MAH shall agree with each member state prior to marketing of Lenalidomide Accord for set-up of national measures to assess for the effectiveness of and compliance with the 'Pregnancy Prevention Programme' (Category 3).

Routine pharmacovigilance including analysis of ADR reports to assess compliance with SmPC recommendations will allow assessing and judging the success of the risk minimisation measures. Effectiveness of the programme will be analysed by MAH as per the requirements for submission of periodic safety update reports (PSUR) for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Additional risk minimisation 3

Patient Educational Materials (Educational brochure for patients, Patient alert card and Risk awareness forms)

Objectives:

To increase an awareness of patients regarding risk of teratogenicity and second primary malignancies with use of lenalidomide.

Rationale for the additional risk minimisation activity:

To minimise the reporting frequency of ADR related with teratogenicity and second primary malignancies risk by increasing an awareness of patients.

Target audience and planned distribution path:

Patients or care taker of patients.

Post approval of this MA application. MAH may distribute 'Patient Brochure" to above mentioned target audience as per national requirement.

Plans to evaluate the effectiveness of the interventions and criteria for success:

[redacted]

Routine pharmacovigilance including analysis of ADR reports to assess compliance with SmPC recommendations will allow assessing and judging the success of the risk minimisation measures. Effectiveness of the programme will be analysed by MAH as per the requirements for submission of periodic safety update reports (PSUR) for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

[redacted]

V.3 Summary of risk minimisation measures

Table 4: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Teratogenicity	Routine risk minimisation measures: • SmPC Sections: 4.3, 4.6, 4.8 and 5.3 • PIL Section: 2 • SmPC Section 4.4: warnings and precautions for use o Criteria for women of non-childbearing potential o Counseling o Contraception o Pregnancy testing o Precautions for men o Additional precautions o Reference to educational materials, prescribing and dispending restrictions • The pack is based on a maximum 4-week supply of capsules to ensure that FCBP (Females of child bearing potential) are required to obtain a new monthly prescription with a medically supervised pregnancy test. • Prescription only status of the product	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Specific follow-up questionnaires have been proposed for Teratogenicity. Additional pharmacovigilance activities: Pregnancy prevention programme for Lenalidomide Accord shall be implemented as Category 3 study.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: • Pregnancy Prevention Programme (PPP) • HCP Brochure • Treatment algorithm • Pregnancy reporting form • Patient card • Patient brochure • Risk awareness form	
Serious infection due to neutropenia	Routine risk minimisation measures: • SmPC Section: 4.8 • SmPC Section 4.2: Dose reduction advice for neutropenia. • SmPC Section 4.4: Warning of neutropenia, and infection with or without neutropenia, and advice for monitoring patients, including blood testing for neutropenia; Advice that patients should report febrile episodes promptly; Advice that HBV status should be established before initiating treatment with lenaliomide and advice to exercise caution when lenalidomide is used in patients previously infected with HBV. In addition, advice that patients should be closely monitored for signs and symptoms of	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Specific follow-up questionnaires have been proposed for neutropenia and infection Additional pharmacovigilance activities: None

[redacted]

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	active HBV infection throughout therapy. • PIL Section 2: Advice to the doctor to check if the patient has ever had hepatitis B infection prior to lenalidomide treatment. • Prescription only status of the product. Additional risk minimisation measures: None	
Second primary malignancies (SPM)	Routine risk minimisation measures: • SmPC Section: 4.8 • PIL Section: 4 • SmPC Section 4.4: This section highlights the risk of SPM, and advises standard cancer screening before and during lenalidomide use, with instigation of treatment as necessary. • Prescription only status of the product Additional risk minimisation measures: • HCP Brochure • Risk awareness forms	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Specific follow-up questionnaires have been proposed Other second primary malignancies (SPM). Additional pharmacovigilance activities: None
Tumour flare reaction (Follicular lymphoma indication and Mantle cell lymphoma)	Routine risk communication: • SmPC Section: 4.8 • PIL Section: 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

[redacted]

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• SmPC Section 4.2: This section includes dose interruption advice for Tumour flare reaction. • SmPC Section 4.4: This section highlights the risk of TFR in lenalidomide-treated patients with CLL and other lymphomas, and warns that tumour flare may mimic disease progression. • Prescription only status of the product. Additional risk minimisation measures: • HCP Brochure	Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Specific follow-up questionnaires have been proposed Tumor flare reaction. Additional pharmacovigilance activities: • None
Important Potential Risks		
Cardiac failure	Routine risk minimisation measures: • SmPC Section: 4.8 • PIL Section: 4 • Prescription only status of the product. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Specific follow-up questionnaires have been proposed for Cardiac failure Additional pharmacovigilance activities: • None

[redacted]

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Cardiac arrhythmias	Routine risk minimisation measures: • SmPC Section: 4.8 • PIL Section: 4 • Prescription only status of the product. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Specific follow-up questionnaires have been proposed for Cardiac arrhythmias Additional pharmacovigilance activities: • None
Ischaemic heart disease (including myocardial infarction)	Routine risk minimisation measures: • SmPC Section: 4.8 • PIL Section: 4 • SmPC Section 4.4: This section highlights the possible occurrence of MI and advises monitoring of patients with known risk factors. • Prescription only status of the product. Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Specific follow-up questionnaires have been proposed for Myocardial infarction

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• None	Additional pharmacovigilance activities: • None
Off-label use	Routine risk minimisation measures: • SmPC Section: 4.4 • Collection of detailed data relating to the indication in order to monitor closely the off-label use within the national territory, is included in SmPC section 4.4. • Prescription only status of the product. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Additional pharmacovigilance activities: • None

[redacted]

Part VI: Summary of the risk management plan

Summary of risk management plan for Lenalidomide Accord hard capsules (2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20mg and 25 mg) (Lenalidomide)

This is a summary of the risk management plan (RMP) for Lenalidomide Accord hard capsules (2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20mg and 25 mg). Throughout this summary product name is referred to as Lenalidomide Accord hard capsules. The RMP details important risks of Lenalidomide Accord hard capsules, how these risks can be minimised, and how more information will be obtained about Lenalidomide Accord hard capsules' risks and uncertainties (missing information).

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

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

Important new concerns or changes to the current ones will be included in updates of Lenalidomide Accord hard capsules RMP.

I. The medicine and what it is used for

Lenalidomide Accord hard capsules is authorised for the treatment of multiple myeloma, Myelodysplastic syndromes, Mantle cell lymphoma and follicular lymphoma (see SmPC for the full indication).

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

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

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

Important risks of Lenalidomide Accord hard capsules, together with measures to minimise such risks and the proposed studies for learning more about Lenalidomide Accord hard capsules' risks, are outlined below.

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

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

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

In the case of Lenalidomide Accord hard capsules, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

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

II.A List of important risks and missing information

Important risks of Lenalidomide Accord hard capsules are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Accord hard capsules. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Teratogenicity • Serious infection due to neutropenia • Second primary malignancies (SPM) • Tumor flare reaction (Follicular lymphoma and Mantle cell lymphoma indication)
Important potential risks	• Cardiac failure • Cardiac arrhythmias • Ischaemic heart disease (including myocardial infarction) • Off-label use
Missing information	• None

II.B Summary of important risks

Important Identified Risks: **Teratogenicity**	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section: 4.3, 4.6, 4.8 and 5.3 • PIL Sections: 2 • SmPC Section 4.4: warnings and precautions for use o Criteria for women of non-childbearing potential o Counseling o Contraception o Pregnancy testing o Precautions for men o Additional precautions o Reference to educational materials, prescribing and dispending restrictions • The pack is based on a maximum 4-week supply of capsules to ensure that FCBP (Females of child bearing potential) are required to obtain a new monthly

	prescription with a medically supervised pregnancy test. • Prescription only status of the product Additional risk minimisation measures: • Pregnancy Prevention Programme (PPP) • HCP Brochure • Treatment algorithm • Pregnancy reporting form • Patient card • Patient brochure • Risk awareness forms
Important Identified Risk: Second primary malignancies (SPM)	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section: 4.8 • PIL Section: 4 • SmPC Section 4.4: This section highlights the risk of SPM, and advises standard cancer screening before and during lenalidomide use, with instigation of treatment as necessary. • Prescription only status of the product Additional risk minimisation measures: • HCP Brochure • Risk awareness forms
Important Identified Risk: Tumour flare reaction (Follicular lymphoma and Mantle cell lymphoma indication)	
Risk minimisation measures	Routine risk communication: • SmPC Section: 4.8 • PIL Section: 2

[redacted]

	• SmPC Section 4.2: This section includes dose interruption advice for Tumour flare reaction. • SmPC Section 4.4: This section highlights the risk of TFR in lenalidomide-treated patients with CLL and other lymphomas, and warns that tumour flare may mimic disease progression. • Prescription only status of the product. <u>Additional risk minimisation measures:</u> • HCP Brochure

II.C Post-authorisation development plan

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

Pregnancy prevention programme (PPP) for Lenalidomide Accord shall be implemented as Category 3 study to investigate teratogenicity an important identified risk and to evaluate the effectiveness of PPP as risk minimisation activities, as a conditions of the marketing authorisation or specific obligation for Lenalidomide Accord hard capsules.

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

There are no studies required for Lenalidomide Accord hard capsules.

[redacted]

Part VII: Annexes

Table of contents

[redacted]

Annex 4 - Specific adverse drug reaction follow-up forms

MAH has developed following targeted follow-up questionnaires for following risks;

1. Teratogenicity (pregnancy follow-up form)
2. Serious infection due to neutropenia
3. Second primary malignancies (SPM)
4. Tumour flare reaction
5. Cardiac arrhythmia and ECG changes
6. Cardiac failure
7. Myocardial infarction
8. Acute myeloid leukaemia and myelodysplastic syndromes

Targeted Follow-up Questionnaire for Pregnancy Background

(Patient or Partner of Patient)

***PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.**

PATIENT DETAILS:

Initials	Age	Weight	Height	Date of Birth	Hospital Ref.

SPECIFIC QUESTIONS FOR EVENT TERATOGENICITY:

Obstetrician Information (Please provide)			
OBSTETRICIAN NAME:			
ADDRESS:	CITY, STATE, ZIP, COUNTRY:		
PHONE No.:	FAX No.:		
Partner of Patient information ☐Not applicable			
Date of Birth:	**Ethnicity:** ☐ White ☐ Black ☐ Asian ☐ Other, Specify_____		
Patient Treatment information: Lenalidomide			
Lot No:	Expiry Date:	Dose:	Frequency:
Route:	Start Date:	Stop Date:	
Indication for use:			
Cytogenic abnormalities: ☐ No ☐ Yes If Yes, Specify_____			

Current Pregnancy			
Date of last menstrual period:		Estimated delivery date:	
PREGNANCY TEST	DATE	REFERENCE RANGE	RESULT
Urine Qualitative			
Serum Quantitative			

Prenatal tests		
	DATE	RESULT
Ultrasound		
Ultrasound		

Ultrasound		
Amniocentesis		
Maternal serum AFP		

Pregnancy History		
No of previous pregnancies: Date of last pregnancy:	No of full-term births:	No of pre-term birth:
No of fatal deaths:	No of living children:	No of abortion: 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 stillbirth or spontaneous abortion occur in any previous pregnancy? ☐ No ☐ Yes ☐ Unknown

1) If Yes, in what week of pregnancy did the stillbirth or spontaneous abortion occur? _____Week

2) Was there any birth defect noted? ☐ No ☐ Yes

if yes, please specify: _____

Relevant medical history ☐ No ☐ Yes If Yes, Specify_____			
Medical History	Date of Diagnosis	Medical History	Date of Diagnosis

Social history	
Alcohol Use ☐ No ☐ Yes, If yes, amount/unit consumed per day:	
Tobacco Use ☐ No ☐Yes	IV OR recreational drug use: ☐ No ☐ Yes, specify:

Family history

CONGENITAL ABNORMALITIES ☐ No ☐ Yes, Specify:_____

[redacted]

If there is a family history of congenital abnormalities, was there a consultation with a Geneticist? ☐ No ☐ Yes, Specify:_____
Environmental Exposure (e.g. RADIATION, CHEMICAL EXPOSURE) ☐ No ☐ Yes, Specify:_____

Event(s)	Onset date	Stop Date/ Ongoing	Serious		Causal relationship to Lenalidomide product	
			Y/N	Seriousness criteria*	Y/N	If No, what medication, disease states, etc played a role in the event?

*****Seriousness 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

SUSPECTED DRUG(S):

Drug/Brand Name	Manufacturer & Batch No.	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.						
2.						

ACTION TAKEN WITH SUSPECTED DRUGS:

○ Dose Decreased	○ Dose Increased	○ Drug withdrawn	○ Dose not changed
○ Unknown			

CONCOMITANT MEDICATIONS (incl. herbal or self-medication, dietary supplements and OTC):

Drug/Brand Name	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.					
2.					

[redacted]

3.					

Root cause of Pregnancy:

1. What forms of birth control was your patient using 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

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

☐ No, please proceed to Question 5

☐ Yes, please answer Question 3, Question 4, Question 5, and Question 6

3. If applicable per Question 2, how often did your patient have unprotected sexual intercourse?

☐ Multiple times

☐ Once a week

☐ Once every 2 weeks

☐ Once a month

☐ Not at all

☐ Other, specify_____

4. If applicable per Question 2, why did your patient and/or their partner interrupt or stop using contraception?

☐ Wanted a child

☐ Partner disapproved

☐ Side effects

[redacted]

☐ Health concerns

☐ Inconvenient to use

☐ Other, specify_____

5. **Please ask your patent if they received the Lenalidomide Accord Patient Information (e.g. Medication Guide or patient leaflet).**

☐ No, please proceed to Question 5.3

☐ Yes, please answer the question 5.1

5.1 Please ask your patient if they read the Lenalidomide Accord Patient Information (e.g. Medication Guide or patient leaflet).

☐ No, please proceed to Question 5.3

☐ Yes, please answer Question 5.2

5.2 Please ask your patient if they understood the information in the Lenalidomide Accord Patient Information (e.g. Medication Guide or patient leaflet).

☐ No, please proceed to Question 5.3

☐ Yes, please answer Question 5.2

5.3 Please ask your patient where most of their knowledge about contraception during lenalidomide accord use came from?

☐ **Physician who prescribed Lenalidomide Accord**

☐ **Patient guide to the Lenalidomide REMS program**

☐ **Lenalidomide Accord Patient information (e.g. Medication Guide or patient leaflet)**

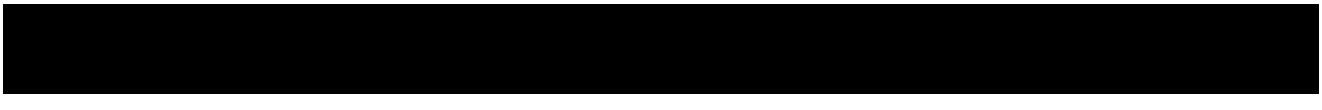
☐ **Other, specify: _____**

6. **Please ask your patient if they felt that they and their partner had a good understanding of the risk of pregnancy during Lenalidomide Accord use.**

☐ Yes

☐ No

☐ Don't know



REPORTER DETAILS:

Title, Name & Surname	Occupation	Signature	Date

Postal Address: Postcode:	Email:	Tel No.

Targeted Follow Up Questionnaire for Pregnancy Follow-Up

(Patient or Partner of Patient)

***PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.**

Name of Patient or Pregnant Partner of Male Patient:_____

Current pregnancy		
Prenatal Test	**Date**	**Result**
Ultrasound		
Ultrasound		
Ultrasound		
Amniocentesis		
Maternal Serum AFP		
Other Tests, Specify:		

Pregnancy Type

☐ Singleton ☐ Twin ☐ Triplet ☐ Other, specify:_____

Medication/Treatments (including herbal, alternative and over-the-counter medicines and dietary supplements) during pregnancy:

Drug	**Start Date**	**Stop Date/ Continuing**	**Indication**
1.			
2.			
3.			

Adverse Event(s) during pregnancy						
Event(s)	**Onset date**	**Stop Date/ Ongoing**	**Serious**		**Causal relationship to Lenalidomide product**	
			Y/N	Seriousness criteria*	Y/N	If No, what medication, disease states, etc played a role in the event?

*****Seriousness 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

Reporter details:

Title, Name & Surname	Occupation	Signature	Date
Postal Address: Postcode:	Email:	Tel No.	

[redacted]

Targeted Follow Up Questionnaire for Pregnancy Outcomes

(Patient or Partner of Patient)

*PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.

PATIENT DETAILS:

Initials	Age	Weight	Height	Date of Birth	Hospital Ref.

Partner of Patient Information: ☐ Not applicable	
Date of Birth:	**Ethnicity:** ☐ White ☐ African-American ☐ Asian ☐ Other, Specify_____

Pregnancy Type

☐ Singleton ☐ Twin ☐ Triplet ☐ Other, specify:_____

PREGNANCY OUTCOME:

DATE OF DELIVERY:			**GESTATION AGE AT DELIVERY:**
DELIVERY DETAILS	NO	YES	ADDITIONAL COMMENTS
Normal	☐	☐	
C-Section	☐	☐	
Induced	☐	☐	
Assisted (e.g., forceps)	☐	☐	
Elective termination	☐	☐	Date:
Spontaneous abortion (≤20 weeks)	☐	☐	Weeks from LMP:
Fetal death/Still birth (> 20 weeks)	☐	☐	
Were the products of conception examined?	☐	☐	If yes, was the fetus normal? ☐ Yes ☐ No ☐ Unknown If no, describe: _____ _____

Obstetrics Information			
	NO	YES	

[redacted]

Complications During Pregnancy	☐	☐	If Yes Specify: _____ _____
Complications During labor/Delivery	☐	☐	If Yes Specify: _____ _____
Post-partum Maternal Complications	☐	☐	If Yes Specify: _____ _____

Fetal Outcome

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

Sex: ☐ Male ☐ Female **Birth Weight**: ____lbs____ oz__ ***or***_____ Kg **Length:** _____ inches ***or*** _____cm

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

REPORTER DETAILS:

Title, Name & Surname	Occupation	Signature	Date
Postal Address: Postcode:	Email:	Tel No.	

Targeted follow up questionnaire for Pregnancy Outcomes

(Patient or Male Patient of Pregnant Partner)

***PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.**

Date: _____

Name of the patient or name of the Male patient partner**:** _____

Please provide the outcome of your or your outcome of partner's pregnancy.

☐ Normal Baby

☐ Abnormal baby, please specify defect _____

☐ Therapeutic abortion, please specify any abnormality of the fetus if known: _____

_____

☐ Spontaneous abortion or miscarriage, please specify any abnormality of the fetus if known:

_____

Reporter Details:

Title, Name & Surname	Occupation	Signature	Date

Postal Address: Postcode:	Email:	Tel No.

[redacted]

Targeted Follow Up Questionnaire for Infant Follow-Up

(Primary Care Physician or Pediatrician)

***PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.**

Date: _____

Age in months: _____

Weight (at the time of assessment): _____lbs _____oz ***or*** _____kg

Length (at the time of this assessment): _____inches ***or*** _____cm

Name of Patient or Name of Male Patient of Partner (Mother): _____

Name of Infant (if known): _____

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

Anomalies Diagnosed Since Initial Report: _____

☐ None

Developmental Assessment: _____

Is the child developing normally for his/her age? ☐ Yes ☐ No

If no, please define your concern regarding any developmental issues or abnormalities:

_____

_____

Birth Defects/Anomalies:

New birth defects or anomalies noted since previous report? ☐Yes ☐ No

If Yes, please list the birth defects/anomalies below:

Birth Defect/ anomaly	Was the defect/ Anomaly Attributed to Lenalidomide accord Therapy? (Y/N/Unknown)	Factors that may have Contributed to this Outcome: (e.g., family history, Maternal age, besity, Alcohol consumption during Pregnancy, etc.)	Defect/ Anomaly Noted Prior to Birth? (Y/N)	Infant Age when Defect/ Anomaly Was Noted (specify Weeks or Months)

[redacted]

Infant illnesses, Hospitalisations, Drug therapies:

Infant Illnesses	Hospitalised?	Drug Therapies
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	

Reporter details:

Title, Name & Surname	Occupation	Signature	Date
Postal Address: Postcode:	Email:	Tel No.	

[redacted]

Targeted Follow Up Questionnaire for Neutropenia

***PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.**

PATIENT DETAILS:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

If female, is the patient pregnant? **Yes / No**	If yes, Date of Last Menstrual Period:	Expected Delivery Date:

SUSPECTED DRUG(S):

Drug/Brand Name	Manufacturer & Batch No.	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.						
2.						

DETAILS OF SUSPECTED ADVERSE REACTION(S):

Date reaction started: 1) 2)	Date reaction stopped: 1) 2)

Please describe the reaction and details of any treatment given or investigation performed.	Outcome: ○ Recovered ○ Not Recovered ○ Recovered with Sequel ○ Recovering ○ Fatal ○ Unknown

SERIOUSNESS OF ADVERSE REACTION(S):

Do you consider the reaction to be serious?	○ Yes	○ No
If Yes, Reason for Seriousness: ○ Patient Died ○ Involved/Prolonged Hospitalisation	○ Life Threatening ○ Disability/Incapacity	○ Congenital Abnormality ○ Medically Significant

[redacted]

ACTION TAKEN WITH SUSPECTED DRUGS:

○ Dose Decreased	○ Dose Increased	○ Drug withdrawn	○ Dose not changed
○ Unknown			

CONCOMITANT MEDICATIONS (incl. herbal or self-medication, dietary supplements and OTC):

Drug/Brand Name	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.					
2.					
3.					

SPECIFIC QUESTIONS FOR EVENT NEUTROPENIA:

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

Date	Test	Pre-treatment value	AE onset value	AE Resolution value	Normal low	Normal high
	WBC					
	ANC					

2. What treatments were given for the neutropenia? Please include dates.

_____

_____

3. Did the patient receive G-CSF? GM-CSF?
☐ No ☐ Yes

If yes, Please provide details_____

4. Did your patient experience an infection in association with the neutropenia?
☐ No ☐ Yes

5. If yes, please provide location of infection.

_____

_____

6. Does the patient have a history of recurrent infection?

[redacted]

☐ No ☐ Yes

Please explain.

_____

_____

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

_____

_____

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

_____

_____

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

_____

_____

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

_____

_____

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

_____

_____

REPORTER DETAILS:

Title, Name & Surname	Occupation	Signature	Date

[redacted]

Postal Address: Postcode:	Email:	Tel No.

Targeted Follow-Up Questionnaire for Second Primary Malignancy

***PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.**

PATIENT DETAILS:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

If female, is the patient pregnant? **Yes / No**	If yes, Date of Last Menstrual Period:	Expected Delivery Date:

SUSPECTED DRUG(S):

Drug/Brand Name	Manufacturer & Batch No.	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.						
2.						

DETAILS OF SUSPECTED ADVERSE REACTION(S):

Date reaction started: 1) 2)	Date reaction stopped: 1) 2)

Please describe the reaction and details of any treatment given or investigation performed.	Outcome: ☐ Recovered ☐ Not Recovered ☐ Recovered with Sequel ☐ Recovering ☐ Fatal ☐ Unknown

SERIOUSNESS OF ADVERSE REACTION(S):

Do you consider the reaction to be serious? ☐ Yes ☐ No

If Yes, Reason for Seriousness:

☐ Patient Died ☐ Life Threatening ☐ Congenital Abnormality

☐ Involved/Prolonged Hospitalisation ☐ Disability/Incapacity ☐ Medically Significant

ACTION TAKEN WITH SUSPECTED DRUGS:

☐ Dose Decreased ☐ Dose Increased ☐ Drug withdrawn ☐ Dose not changed

☐ Unknown

CONCOMITANT MEDICATION (incl. herbal or self-medication):

Drug/Brand Name	**Route of Admin**	**Daily Dosage**	**Indication**	**Date Started**	**Date Stopped**
1.					
2.					

SPECIFIC QUESTIONS FOR EVENT SECOND PRIMARY MALIGNANCIES (SPM):

[redacted]

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

Core questions for follow-up of SPMs:

1. Dates of treatment in regards to the event

_____

2. Dates of the underlying disease's diagnosis

_____

3. Stage of the underlying disease treated with Lenalidomide Accord at baseline, the end of treatment if applicable, and at the time of the event with supportive documentation if available

_____

_____

4. Previous history of malignancies (personal/familial) with estimated dates

_____

_____

5. Underlying medical history and concomitant diseases

_____

_____

6. Environmental exposure e.g. atmospheric pollutants/toxic chemicals (pesticides, herbicides, benzene, solvents); occupation/hobbies

_____

_____

7. Tobacco, alcohol abuse?

_____

[redacted]

8. Date of diagnosis of SPM (specify malignancy or diagnosis if known). Please provide date of first clinical symptoms SPM.

_____

9. Full SPM (specify malignancy or diagnosis if known) biopsy reports with exact stage. If not available please provide the detailed results

_____

_____

10. Treatment of SPM (specify malignancy or diagnosis if known)

_____

_____

In addition to the Core Questions specific information should be requested based on the risk factors for individual types of cancer

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

_____

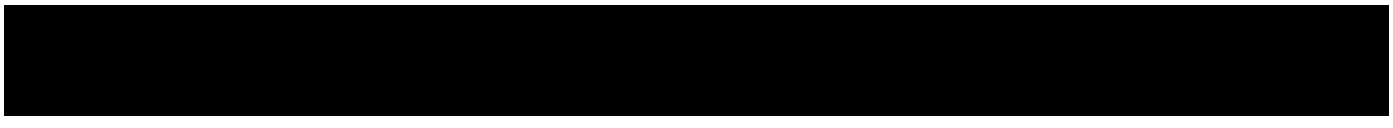
_____

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 ☐

Length of time_____ Number of cigarettes/days _____ Age at starting_____

Gender_____ Product smoked _____ Depth of inhalation_____

☐ 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),

Test	**Result**
Biopsy	
Immunohistochemistry	
Flow cytometry	
Cytogenetics	
Reverse transcriptase polymerase chain reaction	
Fluorescence in situ hybridisation (FISH)	
Next generation sequencing	

Lung Cancer:

- Smoking history –

  Length of time_____ Number of cigarettes/days _____ Age at starting_____

  Gender_____ Product smoked _____ Depth of inhalation_____

- Pre-existing pulmonary disease ☐

- Family history of lung cancer ☐

Lymphoma:

- Medical conditions that compromise the immune system –

  ☐ HIV/AIDS ☐ Autoimmune diseases ☐ Diseases requiring immune suppressive therapy-organ transplant

- Infection with

  ☐ HIV ☐ Epstein-Barr virus+++ ☐ Helicobacter pylori

  ☐ Hepatitis B or C ☐ Human T-lymphotropic virus type I ☐ Burkitt's lymphoma

Thyroid Cancer:

- Personal or family history of thyroid and/or autoimmune diseases

  ☐ Hypo or hyperthyroidism ☐ Goiter ☐ Benign thyroid nodules

  ☐ Hashimoto's disease ☐ Graves disease

- Family history of

  ☐ Familial medullary thyroid cancer ☐ Multiple endocrine neoplasia

  ☐ Familial adenomatous polyposis

- Living in iodine deficient area ☐
- History of radiation exposure ☐

Breast Cancer:

- Receptor status of the tumor

  ☐ ER ☐ PR ☐ Her2/neu

- Age at onset of menses _____ and age of menopause_____
- Number of pregnancies _____ and age at first birth _____
- History of breastfeeding children _____
- Use of oral contraceptives or hormone replacement therapy _____
- Obesity ☐
- Ethnic group _____
- Economic status _____
- Dietary iodine deficiency _____

Ovarian Cancer:

[redacted]

- Number of pregnancies _____ and childbearing status _____
- History of hormone replacement therapy _____
- History of breast cancer _____

Uterine Cancer:

- Age at onset of menses _____ and age of menopause _____
- Number of pregnancies _____
- Use of oral contraceptives _____
- Obesity ☐

Colon Cancer:

- Family or personal history of adenomatous polyposis (FAP) ☐
- Family or personal history of Lynch syndrome (Hereditary nonpolyposis colorectal cancer) ☐
- Diet

  ☐ High in red meat and animal fat ☐ Refined carbohydrates

  ☐ Low-fiber diet ☐ 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
- HIV status _____

Gastric Cancer:

- Diet

  ☐ Rich in pickled vegetables ☐ Salted fish ☐ Salt ☐ Smoked meats
- Helicobacter pylori infection ☐
- Obesity ☐
- Previous gastric surgery
- ☐ Pernicious anemia ☐ Adenomatous polyps ☐ Gastric ulcer

[redacted]

- Chronic atrophic gastritis ☐
- Radiation exposure _____
- History of alcohol use/smoking ☐

Oesophageal Cancer:

- Genetic causes - tylosis (hyperkeratosis palmaris et plantaris)
- Alcohol use/smoking _____
- History of

  ☐ Chronic or acute inflammation (e.g. GERD, Barrett's esophagus, caustic ingestion)

  ☐ Achalasia (esophageal motility disorder)
- Human papilloma virus ☐
- Sclerotherapy ☐
- Plummer-Vinson syndrome (dysphagia, associated with iron deficiency anemia) ☐

Liver cancer:

- History of cirrhosis (including alcoholic, biliary cirrhosis), other chronic liver dysfunction ☐
- History of alcohol use/smoking _____
- Hepatitis B, C _____
- Hemochromatosis ☐
- Indigestion of food contaminated with fungal aflatoxins (in subtropical regions) ☐

Pancreatic Cancer:

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

Renal Cancer (renal cell carcinoma):

- Smoking ☐

  Length of time_____ Number of cigarettes/days _____ Age at starting_____

  Gender_____ Product smoked _____ Depth of inhalation_____
- Obesity ☐

[redacted]

- Hypertension ☐
- Phenacetin-containing analgesics taken in large amounts ☐
- History of renal transplantation ☐
- Exposure to radiopaque dyes, asbestos, cadmium, and leather tanning and petroleum products ☐
- Inherited VHL disease (von Hippel-Lindau disease), Adult polycystic kidney disease, Tuberous sclerosis ☐

Bladder Cancer:

- Smoking ☐

  Length of time_____ Number of cigarettes/days _____ Age at starting_____

  Gender_____ Product smoked _____ Depth of inhalation_____
- Industrial exposure to aromatic amines in dyes, paints, solvents, leather dust, inks, combustion products, rubber, and textiles ☐
- Occupation - painting, driving trucks, and working with metal ☐
- Prior spinal cord injuries with long-term indwelling catheters ☐

Prostate Cancer:

- Ethnic group
- Smoking ☐

  Length of time_____ Number of cigarettes/days _____ Age at starting_____

  Gender_____ Product smoked _____ Depth of inhalation_____
- History of high-grade prostatic intraepithelial neoplasia (PIN) ☐
- Genome changes-deletion of chromosome 3 and fusion of TMPRSS2 and ERG genes ☐
- Testosterone level
- History of sexually transmitted diseases ☐
- History of vasectomy ☐
- History of exposure to cadmium ☐
- History of genitor-urinary infections ☐

Head and Neck Cancer:

- Smoking and alcohol use ☐
- Prolonged sun exposure ☐
- Exposure to Human papilloma virus (HPV) or Epstein-Barr virus (EBV) ☐

- Ethnic group
- History of poor oral hygiene and/or poor nutrition ☐
- Exposure to asbestos, wood dust, paint fumes or chemicals ☐
- History of Gastroesophageal reflux disease (GERD) or laryngopharyngeal reflux disease (LPRD) ☐

Brain tumors (gliomas and menigiomas):

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

Larynx Cancer:

- Smoking history, alcohol use ☐
- Asbestos exposure ☐
- Any activity requiring loud speech, exposure to sudden and frequent temperature changes ☐
- Frequent hoarseness and persistent cough ☐
- Persistently swollen neck glands ☐
- Tonsillectomy and laryngeal surgery ☐

Nasal and Paranasal Sinus Cancer:

- Woodworking, any dust/flour chronic exposure ☐
- History of Infection with human papillomavirus (HPV) ☐
- Smoking ☐

  Length of time_____ Number of cigarettes/days _____ Age at starting_____

  Gender_____ Product smoked _____ Depth of inhalation_____

Mouth and Oropharyngeal Cancer:

- Smoking ☐
- Alcohol use ☐
- History of poor oral hygiene ☐
- Chronic mucosal /gum irritation /ill-fitting dentures ☐
- Betel-Nut chewing (Indian Population) ☐

- History of syphilis or viral infection ☐
- Impaired immunity -AIDS, transplant with anti-rejection drug ☐
- Precancerous mouth plaques -Leukoplakia or erythroplasia ☐
- History of cancer of the aero digestive tract ☐

Melanoma

- 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 condition- Dysplastic nevus, Xeroderma pigmentosum, nevoid basal cell carcinoma syndromes ☐
- Skin type-fair (pale) skin -burns easily, freckles ☐
- Eye colour-blue, green or gray, Hair color -Blond or red
- Use of medication causing sensitivity to sun -antibiotics, hormones, antidepressants ☐
- Immune system depression –AIDS, Leukemias ☐
- Exposure to arsenic, coal tar or creosote ☐
- For eye localisation: History of oculodermal melanocytosis or Dysplastic nevus syndrome ☐
- Ethnic group
- History of prolonged sun exposure (UV radiation) ☐

REPORTER DETAILS:

Title, Name & Surname	Occupation	Signature	Date
Postal Address: Postcode:	Email:		Tel No.

[redacted]

Targeted follow-up questionnaires for Tumor flare reaction

***PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.**

PATIENT DETAILS:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

If female, is the patient pregnant? **Yes / No**	If yes, Date of Last Menstrual Period:	Expected Delivery Date:

SUSPECTED DRUG(S):

Drug/Brand Name	Manufacturer & Batch No.	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.						
2.						

DETAILS OF SUSPECTED ADVERSE REACTION(S):

Date reaction started: 1) 2)	Date reaction stopped: 1) 2)

Please describe the reaction and details of any treatment given or investigation performed.	Outcome: ○ Recovered ○ Not Recovered ○ Recovered with Sequel ○ Recovering ○ Fatal ○ Unknown

SERIOUSNESS OF ADVERSE REACTION(S):

Do you consider the reaction to be serious?	○ Yes	○ No
If Yes, Reason for Seriousness: ○ Patient Died ○ Involved/Prolonged Hospitalisation	○ Life Threatening ○ Disability/Incapacity	○ Congenital Abnormality ○ Medically Significant

[redacted]

ACTION TAKEN WITH SUSPECTED DRUGS:

○ Dose Decreased	○ Dose Increased	○ Drug withdrawn	○ Dose not changed
○ Unknown			

CONCOMITANT MEDICATION (incl. antiemetics, herbal or self-medication, dietary supplements and OTC):

Drug/Brand Name	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.					
2.					
3.					

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):

_____

_____

Other Etioloical factors: ☐ Yes (please complete below) ☐ No ☐ Unknown

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

Please include familial history of malignancies, environmental exposure, blood transfusion dependence status.

_____

_____

☐ Family history (please specify):_____
☐ Drug/alcohol/tobacco abuse: _____
☐ Other (please specify): _____

Additional questions:

[redacted]

Provide Lenalidomide Accord dosing with therapy start date, and all doses prior to the tumor flare reaction.

_____

_____

Please confirm the chemotherapy indication.

_____

_____

Tumor burden (to specify) or disease stage at baseline and at the time of the event.

_____

_____

Details on the associated symptoms :
Fever :_____(please provide temperature value)
Pain:_____(specify)
Rash:_____(details on zones)
Tender lymph nodes/ swelling:_____(specify location)
Tender liver or spleen
Elevated WBC counts: _____
Other: _____(to specify)

Any complication: _____ (specify).

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

_____

_____

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

_____

_____

Does this patient have a history of previous tumor flare?
☐ Yes ☐ No ☐ Unknown
If yes, please describe

_____

_____

Provide the action taken with Lenalidomide Accord in response to the tumor flare reaction:
☐ None
☐ Permanently Discontinued Stop date: _____
☐ Temporarily Interrupted Stop date: _____
☐ Dose Reduced Date and new dose:_____

[redacted]

☐ Dose Increased Date and new dose:_____

Did the event abate after discontinuing Lenalidomide Accord? ☐ Yes ☐ No

Was Lenalidomide Accord product re-introduced? ☐ Yes ☐ No
Provide restart date and dosing:

_____

_____

Provide the action taken with concomitant chemotherapy (to specify):_____
☐ None
☐ Permanently Discontinued Stop date: _____
☐ Temporarily Interrupted Stop date: _____
☐ Dose Reduced Date and new dose:_____
☐ Dose Increased Date and new dose:_____

Did the event abate after discontinuing concomitant chemotherapy? ☐ Yes ☐ No
Was concomitant chemotherapy re-introduced? ☐ Yes ☐ No
Provide restart date and dosing:

_____

_____

Treatment of the tumor flare (details).

_____

_____

Response to treatment

_____

_____

REPORTER DETAILS:

Title, Name & Surname	Occupation	Signature	Date

Postal Address: Postcode:	Email:	Tel No.

[redacted]

Targeted Follow Up Questionnaire for Cardiac Arrhythmia and ECG Changes

***PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.**

PATIENT DETAILS:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

If female, is the patient pregnant? **Yes / No**	If yes, Date of Last Menstrual Period:	Expected Delivery Date:

SUSPECTED DRUG(S):

Drug/Brand Name	Manufacturer & Batch No.	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.						
2.						

DETAILS OF SUSPECTED ADVERSE REACTION(S):

Date reaction started: 1) 2)	Date reaction stopped: 1) 2)

Please describe the reaction and details of any treatment given or investigation performed.	Outcome: ○ Recovered ○ Not Recovered ○ Recovered with Sequel ○ Recovering ○ Fatal ○ Unknown

SERIOUSNESS OF ADVERSE REACTION(S):

Do you consider the reaction to be serious?	○ Yes	○ No
If Yes, Reason for Seriousness: ○ Patient Died ○ Involved/Prolonged Hospitalisation	○ Life Threatening ○ Disability/Incapacity	○ Congenital Abnormality ○ Medically Significant

[redacted]

ACTION TAKEN WITH SUSPECTED DRUGS:

○ Dose Decreased	○ Dose Increased	○ Drug withdrawn	○ Dose not changed
○ Unknown			

CONCOMITANT MEDICATION (incl. antiemetics, herbal or self-medication, dietary supplements and OTC):

Drug/Brand Name	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.					
2.					
3.					

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

_____

_____

Other Etioloical factors: ☐ Yes (please complete below) ☐ No ☐ 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): _____

SPECIFIC QUESTIONS FOR CARDIAC ARRHYTHMIA AND ECG CHANGES:

- Please provide brief description of cardiac arrhythmia or ECG changes including the type and clinical sign/symptoms observe and including start date and stop date.

  Types of arrhythmia / ECG change: _____

  _____

  Clinical sign/symptoms if present (if none please state): _____

  _____

  Start date _____ Stop date _____

[redacted]

- Does the patient have a relevant cardiac history? If yes, please specify in box below, if no please state

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

Medical History	Onset date/ Duration

- Please provide the available results of diagnostics workup (Use separate sheet if necessary)

Test	Baseline		Event onset/ worst		Recovery/ Latest	
	Date	Result	Date	Result	Date	Result
EKG findings						
Echocardiogram						
Chest X-ray						
Holter stress test						

- Please provide the available results of diagnostic workup (always ask for the result of serum potassium and magnesium studies- use separate sheet if necessary)

Laboratory Testing	Reference range	At baseline		At Event onset/ worst		Recovery/ Latest	
		Date	Result	Date	Result	Date	Result
CK							
CPK-MB							
Troponin							
Hemoglobin							
Metabolic Panel (Specify)							
Serum K+							

[redacted]

Serum Mg 2+							
Phosphorus							
Calcium							
Uric acid							
Creatine							
BUN							

- Please describe specific treatments and interventions of the arrhythmia

_____

_____

REPORTER DETAILS:

Title, Name & Surname	Occupation	Signature	Date

Postal Address: Postcode:	Email:	Tel No.

Targeted follow up questionnaire for Cardiac Failure

***PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.**

PATIENT DETAILS:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

If female, is the patient pregnant? **Yes / No**	If yes, Date of Last Menstrual Period:	Expected Delivery Date:

SUSPECTED DRUG(S):

Drug/Brand Name	Manufacturer & Batch No.	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.						
2.						

DETAILS OF SUSPECTED ADVERSE REACTION(S):

Date reaction started: 1) 2)	Date reaction stopped: 1) 2)

Please describe the reaction and details of any treatment given or investigation performed.	Outcome: ○ Recovered ○ Not Recovered ○ Recovered with Sequel ○ Recovering ○ Fatal ○ Unknown

SERIOUSNESS OF ADVERSE REACTION(S):

Do you consider the reaction to be serious?	○ Yes	○ No
If Yes, Reason for Seriousness: ○ Patient Died ○ Involved/Prolonged Hospitalisation	○ Life Threatening ○ Disability/Incapacity	○ Congenital Abnormality ○ Medically Significant

[redacted]

ACTION TAKEN WITH SUSPECTED DRUGS:

○ Dose Decreased	○ Dose Increased	○ Drug withdrawn	○ Dose not changed
○ Unknown			

CONCOMITANT MEDICATION (incl. herbal or self-medication, dietary supplements and OTC):

Drug/Brand Name	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.					
2.					
3.					

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

_____

_____

Other Etioloical factors: ☐ Yes (please complete below) ☐ No ☐ Unknown

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

_____

_____

☐ Family history (please specify):_____

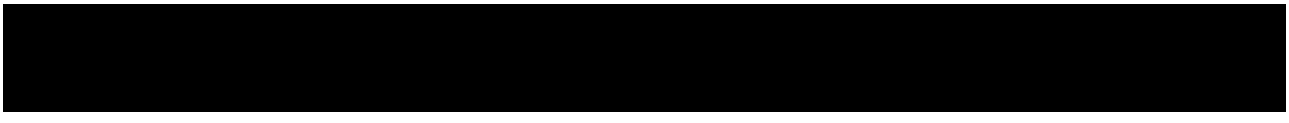
☐ Drug/alcohol/tobacco abuse: _____

☐ Other (please specify): _____

SPECIFIC QUESTIONS FOR EVENT CARDIAC FAILURE:

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 exacerbation of was diagnosed _____

2. Please circle classification of cardiac failure:
   a. Class I (mild) Patients with cardiac disease but without limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or angina pain
   b. Class II (mild) Patients with cardiac disease resulting in slight limitation of physical activity. they are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina pain.
   c. Class III (moderate) Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or angina pain.



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

3. Please provide result of EKG, echocardiogram and ejection fraction including the baseline data and dates.

_____

_____

4. Did the patient receive any recent blood transfusion or IV infusion? ☐ Yes ☐ No

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

_____

_____

5. Please provide the additional laboratory tests surrounding the event:

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					

6. Does the patient have other cardiac history including coronary artery disease, cardiac stents, myocardial infarction, vascular heart diseases, cardiomyopathy, other chemotherapy (previous and ongoing) etc.? please specify:

_____

_____

7. Please provide any associated risk factor including history of hyperlipidaemia, obesity, hypertension, COPD, renal disease, diabetes, sepsis, substance abused etc.

_____

_____

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

_____

_____

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

_____

_____

10. What treatment/interventions were provided to the patient for the cardiac failure? Please specify.

_____

_____

REPORTER DETAILS:

Title, Name & Surname	Occupation	Signature	Date

Postal Address: Postcode:	Email:	Tel No.

Targeted Follow Up Questionnaire for Myocardial Infarction

PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.

PATIENT DETAILS:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

If female, is the patient pregnant? **Yes / No**	If yes, Date of Last Menstrual Period:	Expected Delivery Date:

SUSPECTED DRUG(S):

Drug/Brand Name	Manufacturer & Batch No.	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.						
2.						

DETAILS OF SUSPECTED ADVERSE REACTION(S):

Date reaction started: 1) 2)	Date reaction stopped: 1) 2)

Please describe the reaction and details of any treatment given or investigation performed.	Outcome: ○ Recovered ○ Not Recovered ○ Recovered with Sequel ○ Recovering ○ Fatal ○ Unknown

SERIOUSNESS OF ADVERSE REACTION(S):

[redacted]

Do you consider the reaction to be serious?	○ Yes	○ No
If Yes, Reason for Seriousness: ○ Patient Died ○ Involved/Prolonged Hospitalisation	○ Life Threatening ○ Disability/Incapacity	○ Congenital Abnormality ○ Medically Significant

ACTION TAKEN WITH SUSPECTED DRUGS:

○ Dose Decreased	○ Dose Increased	○ Drug withdrawn	○ Dose not changed
○ Unknown			

CONCOMITANT MEDICATION (incl. herbal or self-medication, dietary supplements and OTC):

Drug/Brand Name	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.					
2.					
3.					

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):

_____

_____

Other Etioloical factors: ☐ Yes (please complete below) ☐ No ☐ Unknown

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

[redacted]

_____

_____

☐ Family history (please specify):_____

☐ Drug/alcohol/tobacco abuse: _____

☐ Other (please specify): _____

Additional questions:

Did the patient have a history of cardiac disease such as coronary artery disease, myocardial infarction, arrhythmia, or congestive heart failure? Please provide the onset dates of diagnosis.

_____

_____

Please provide any risk factors for the myocardial infarction. (hyperlipidemia, hypercholesterolemia, obesity, hypertension, COPD, renal disease, diabetes, sepsis, substance abuse, sedentary life style, immobility, dehydration, etc.).

_____

_____

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

_____

_____

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

_____

_____

Please provide concurrent events/circumstances surrounding the MI.

_____

_____

Did the patient have a history of chest pain?

_____

_____

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

_____

_____

REPORTER DETAILS:

Title, Name & Surname	Occupation	Signature	Date
Postal Address: Postcode:	Email:	Tel No.	

[redacted]

Targeted Follow-Up Questionnaire for Acute Myeloid Leukaemia and Myelodysplastic Syndromes

***PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.**

PATIENT DETAILS:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

If female, is the patient pregnant? **Yes / No**	If yes, Date of Last Menstrual Period:	Expected Delivery Date:

SUSPECTED DRUG(S):

Drug/Brand Name	Manufacturer & Batch No.	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.						
2.						

DETAILS OF SUSPECTED ADVERSE REACTION(S):

Date reaction started: 1) 2)	Date reaction stopped: 1) 2)

Please describe the reaction and details of any treatment given or investigation performed.	Outcome: ○ Recovered ○ Not Recovered ○ Recovered with Sequel ○ Recovering ○ Fatal ○ Unknown

SERIOUSNESS OF ADVERSE REACTION(S):

Do you consider the reaction to be serious? ○ Yes ○ No

[redacted]

If Yes, Reason for Seriousness:

○ Patient Died	○ Life Threatening	○ Congenital Abnormality
○ Involved/Prolonged Hospitalisation	○ Disability/Incapacity	○ Medically Significant

ACTION TAKEN WITH SUSPECTED DRUGS:

○ Dose Decreased	○ Dose Increased	○ Drug withdrawn	○ Dose not changed
○ Unknown			

CONCOMITANT MEDICATION (incl. herbal or self-medication):

Drug/Brand Name	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.					
2.					
3.					

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

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

_____

_____

Other Etioloical factors: ☐ Yes (please complete below) ☐ No ☐ Unknown

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

Please include familial history of malignancies, environmental exposure, blood transfusion dependence status.

_____

_____

[redacted]

☐ Family history (please specify):_____
☐ Drug/alcohol/tobacco abuse: _____
☐ Other (please specify): _____

Additional questions:

Please provide the date [Lenalidomide Accord drug indication, e.g., AML or MDS] was initially diagnosed with stage/classification.

_____

_____

Please provide full bone marrow results as well as full cytogenetics at baseline and at the time of diagnosis of [MDS or AML] with dates. Please specify if this information is not available or not evaluable.

_____

_____

Please specify AML type if not included in the bone marrow or cytogenetics documents. Please specify if this information is not available or not evaluable.

_____

_____

Please also provide the Lenalidomide Accord indication stage/classification at the time of the MDS or AML diagnosis. Please specify if this information is not available or not evaluable. Is there evidence of progression of underlying disease? Please explain.

_____

_____

Please provide changes in transfusion dependence status during disease (Lenalidomide Accord indication) treatment with corresponding dates.

_____

_____

Please provide information on any antineoplastic treatments the patient may have received including radiotherapy with radiation zone for any malignant neoplasm, specifying the indication for this. Please provide duration of treatment with dates and also cumulative dose if available.

[redacted]

_____

_____

Please specify what treatment was received for the AML/MDS.

_____

_____

What was the outcome of AML/MDS? If fatal outcome, please provide circumstances surrounding the death.

_____

_____

[redacted]

Annex 6 - Details of proposed additional risk minimisation activities

1. The MAH shall agree the details of a controlled distribution system with the National Competent Authorities and must implement such programme nationally to ensure that:

- Prior to prescribing (and where appropriate, and in agreement with the National Competent Authority, prior to dispensing) all healthcare professionals who intend to prescribe (and dispense) Lenalidomide Accord are provided with a physician information pack containing the following:
    - Educational health care professional's kit
    - Educational brochures for patients
    - Patient cards
    - Summary of product characteristics (SmPC) and package leaflet and labelling
    - Risk awareness forms

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 product.

3. The MAH should agree the final text of the physician information pack contents with the National Competent Authority in each Member State 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.

<u>Key elements to be included</u>

The Educational Healthcare Professional's Kit

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

- Brief background on lenalidomide
- Maximum duration of treatment prescribed
    - 4 weeks treatment for women with childbearing potential
    - 12 weeks treatment 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 Accord for healthcare professionals and caregivers
- Obligations of the health care professional in relation to the prescribing of Lenalidomide Accord
    - 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 Accord
  - 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 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 Accord.
- 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 physician 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 adequate 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 Accord immediately upon suspicion of pregnancy
  - Need to tell treating doctor immediately upon suspicion of pregnancy
- Safety advice for men
  - The need to avoid foetal exposure

  - The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraception (even if the man has had a vasectomy)
    - During Lenalidomide Accord 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 Accord treatment.
  - That if his partner becomes pregnant whilst he is taking Lenalidomide Accord or shortly after he has stopped taking Lenalidomide Accord he should inform his treating doctor immediately
- Requirements in the event of pregnancy
  - Instructions to stop Lenalidomide Accord immediately upon suspicion of pregnancy, if female patient
  - Need to refer 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 for patients, caregivers and family members
- National or other applicable specific arrangements for a prescription for Lenalidomide Accord to be dispensed
- That the patient must not give Lenalidomide Accord to any other person
- That the patient should not donate blood during therapy (including during dose interruptions) and for at least 7 days after discontinuation of Lenalidomide Accord treatment
- That the patient should tell their doctor about any adverse events
- That any unused capsules should be returned to the pharmacist at the end of the treatment

The following information should also be provided in the appropriate brochure:

Brochure for women patients with childbearing potential

[redacted]

- The need to avoid foetal exposure
- Description of the PPP
- The need for effective contraception and definition of effective contraception
- That if she needs to change or stop using her method of contraception she should inform:
    - The physician prescribing her contraception that she is on lenalidomide
    - The physician prescribing lenalidomide that she has stopped or changed her method of contraception
- Pregnancy test regime
    - Before commencing treatment
    - During treatment (including dose interruptions), at least every 4 weeks except in case of confirmed tubal sterilisation
    - After finishing treatment
- The need to stop Lenalidomide Accord immediately upon suspicion of pregnancy
- The need to contact their doctor immediately upon suspicion of pregnancy

Brochure for male patients

- The need to avoid foetal exposure
- The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraceptions (even if the man has had vasectomy)
    - During Lenalidomide Accord treatment (including dose interruptions)
    - For at least 7 days following final dose
- That if his partner becomes pregnant, he should inform his treating doctor immediately
- That he should not donate semen or sperm during treatment (including during dose interruptions) and for at least for 7 days after discontinuation of Lenalidomide Accord treatment

Patient Card or equivalent tool

The patient card shall contain the following elements:

- Verification that appropriate counselling has taken place
- Documentation of childbearing potential status
- Pregnancy test dates and results
- Check box (or similar) which physician ticks to confirm that patient is using effective contraception (if woman of childbearing potential).
- Pregnancy test dates and results

Risk Awareness Forms

There should be 3 types of risk awareness forms:

- Women of childbearing potential
- Women of non-childbearing potential

- Male patient

All risk awareness forms should contain the following elements:

- teratogenicity warning
- patients receive the appropriate counselling prior to treatment initiation
- affirmation of patient understanding of the risk of lenalidomide and the PPP measures
- date of counselling
- patient details, signature and date
- prescriber name, signature and date
- aim of this document i.e. as stated in the PPP: "The aim of the risk awareness form is to protect patients and any possible foetuses by ensuring that patients are fully informed of and understand the risk of teratogenicity and other adverse reactions associated with the use of lenalidomide. It is not a contract and does not absolve anybody from his/her responsibilities with regard to the safe use of the product and prevention of foetal exposure."

Risk awareness forms for women of childbearing potential should also include:

- Confirmation that the physician has discussed the following:
    - the need to avoid foetal exposure
    - that if she is pregnant or plans to be, she must not take lenalidomide
    - that she understands the need to avoid lenalidomide during pregnancy and to apply effective contraceptive measures without interruption, at least 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 Accord
        - the physician prescribing Lenalidomide Accord 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 Accord 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 Accord
    - 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 Accord
- 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 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 Accord
  - that he should return the unused capsules to the pharmacist at the end of treatment