EU Risk Management Plan for Pomalidomide

No 56/24

RMP version to be assessed as part of this application:

RMP Version number:	V 1.0	
Data lock point for this RMP:	5 April 2024	
Date of final sign off:	3 June 2024	
Rationale for submitting an updated RMP:	Final initial version. RMP was updated according to the latest approved RMP V17.0 (DLP: 07/02/2022) for the reference product Imnovid.	
Summary of significant changes in this RMP:	Part III: Pharmacovigilance Plan	Routine pharmacovigilance activities: - Analysis of Adverse Drug Reactions of Special Interest - Specific Adverse Reaction Follow-up Questionnaires - Expedited Reporting and Follow-up of Pregnancy were included according to the reference product. Monitoring of implementation of PPP as additional pharmacovigilance activity cat 3 was included.
	Part V: Risk Minimisation Measures	Routine and additional risk minimisation measures were structured according to reference product and GVP.
	Part VI: Summary of the RMP	Updated to reflect the above mentioned changes.
	Part VII: Annexes	Annex 4 - Specific adverse drug reaction follow-up forms Annex 6 - Details of proposed additional risk minimisation activities were updated according to the reference product.
Other RMP versions under evaluation:	RMP version number:	Not applicable.
	Submitted on:	Not applicable.
	Procedure number:	Not applicable.
Details of the currently approved RMP:	RMP version number:	Not applicable.
	Approved with procedure:	Not applicable.
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QPPV name:	Ludmila FILIPOVÁ, MD	
QPPV (or delegate) signature:	*The electronic signature is available on file.*	

ZENTIVA

Contact person for this RMP:	[redacted]
E-mail address:	[redacted]
Prepared by:	[redacted]
Validated by:	[redacted]

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List of Abbreviations

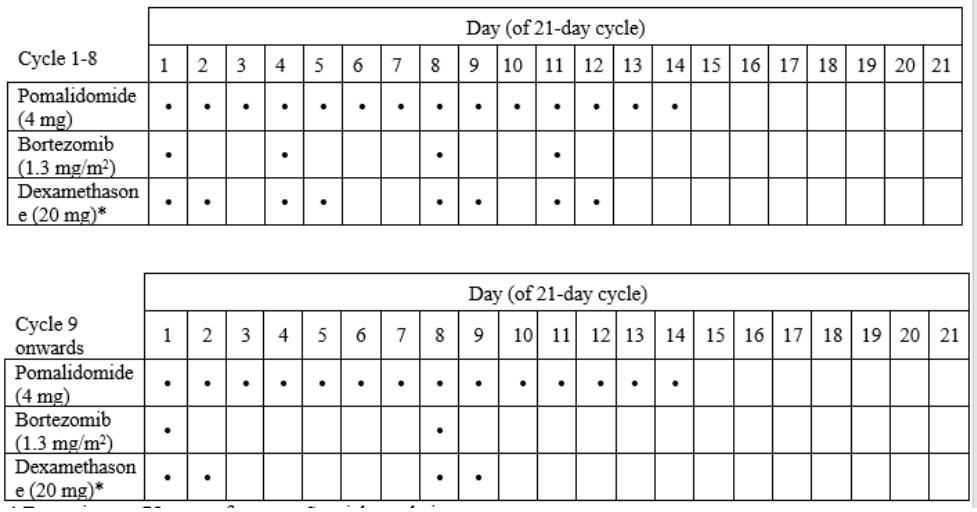
ADR	Adverse drug reaction
AF	Atrial fibrillation
ATC	Anatomical Therapeutic Chemical classification
BCC	Basal cell carcinoma
DHPC	Direct Healthcare Professional Communication
EMA	European Medicines Agency
EU	European Union
EEA	European Economic Area
eCTD	Electronic Common Technical Document
HBV	Hepatitis B virus
INN	International Nonproprietary Name
MAH	Marketing Authorisation Holder
NMSC	Non-melanoma Skin Cancer
PL	Package Leaflet
PPP	Pregnancy Prevention Programme
PSUR	Periodic Safety Update Report
RBC	Red blood cell
RMP	Risk Management Plan
QPPV	Qualified Person for Pharmacovigilance
SCC	Squamous cell carcinoma
SmPC	Summary of Product Characteristics
SPM	Second Primary Malignancies
WBC	White blood cell
WCBP	Women of childbearing potential

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Pomalidomide
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants, Other immunosuppressants, ATC code: L04AX06
Marketing Authorisation Holder	Zentiva k.s.
Medicinal products to which this RMP refers	<4>
Invented name(s) in the European Economic Area (EEA)	Pomalidomide Zentiva 1 mg hard capsules Pomalidomide Zentiva 2 mg hard capsules Pomalidomide Zentiva 3 mg hard capsules Pomalidomide Zentiva 4 mg hard capsules
Marketing authorisation procedure	Centralised
Brief description of the product	<u>Chemical class:</u> Immunosuppressants, Other immunosuppressants, ATC code: L04AX06
	<u>Summary of mode of action:</u> Pomalidomide has direct anti-myeloma tumoricidal activity, immunomodulatory activities and inhibits stromal cell support for multiple myeloma tumour cell growth. Specifically, pomalidomide inhibits proliferation and induces apoptosis of haematopoietic tumour cells. Additionally, pomalidomide inhibits the proliferation of lenalidomide-resistant multiple myeloma cell lines and synergises with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumour cell apoptosis. Pomalidomide enhances T cell- and natural killer (NK) cell-mediated immunity and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. Pomalidomide also inhibits angiogenesis by blocking the migration and adhesion of endothelial cells. Pomalidomide binds directly to the protein cereblon (CRBN), which is part of an E3 ligase complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins-1 (Roc1), and can inhibit the auto-ubiquitination of CRBN within the complex. E3 ubiquitin ligases are responsible for the poly-ubiquitination of a variety of substrate proteins, and may partially explain the pleiotropic cellular effects observed with pomalidomide treatment. In the presence of pomalidomide *in vitro*, substrate proteins Aiolos and Ikaros are targeted for ubiquitination and subsequent degradation leading to direct cytotoxic and immunomodulatory effects. *In vivo*, pomalidomide therapy led to reduction in the levels of Ikaros in patients with relapsed lenalidomide-refractory multiple myeloma.
	<u>Important information about its composition:</u> None.
Hyperlink to the Product Information	Please refer to section 1.3.1 in eCTD.

Indication(s) in the EEA	Current: Pomalidomide Zentiva in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide. Pomalidomide Zentiva in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.
	Proposed (if applicable): Not applicable.
Dosage in the EEA	Current: Treatment must be initiated and monitored under the supervision of physicians experienced in the management of multiple myeloma. Dosing is continued or modified based upon clinical and laboratory findings. Posology • *Pomalidomide in combination with bortezomib and dexamethasone* The recommended starting dose of pomalidomide is 4 mg taken orally once daily on Days 1 to 14 of repeated 21- day cycles. Pomalidomide is administered in combination with bortezomib and dexamethasone, as shown in table 1. The recommended starting dose of bortezomib is 1.3 mg/m^2 intravenous or subcutaneous once daily, on the days shown in table 1. The recommended dose of dexamethasone is 20 mg taken orally once daily, on the days shown in table 1. Treatment with pomalidomide combined with bortezomib and dexamethasone should be given until disease progression or until unacceptable toxicity occurs. **Table 1. Recommended dosing scheme for pomalidomide in combination with bortezomib and dexamethasone**

	 Cycle 1-8 / Day (of 21-day cycle) Pomalidomide (4 mg): • • • • • • • • • • • • • • Bortezomib (1.3 mg/m²): • • • • • Dexamethasone (20 mg)*: • • • • • • • • • • • Cycle 9 onwards / Day (of 21-day cycle) Pomalidomide (4 mg): • • • • • • • • • • • • • • Bortezomib (1.3 mg/m²): • • • Dexamethasone (20 mg)*: • • • • • • * For patients > 75 years of age, see Special populations. • *Pomalidomide in combination with dexamethasone* The recommended starting dose of pomalidomide is 4 mg taken orally once daily on Days 1 to 21 of each 28-day cycle. The recommended dose of dexamethasone is 40 mg taken orally once daily on Days 1, 8, 15 and 22 of each 28-day cycle. Treatment with pomalidomide combined with dexamethasone should be given until disease progression or until unacceptable toxicity occurs. <u>Method of administration</u> Oral use. Pomalidomide Zentiva hard capsules should be taken orally at the same time each day. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, with or without food. If the patient forgets to take a dose of pomalidomide on one day, then the patient should take the normal prescribed dose as scheduled on the next day. Patients should not adjust the dose to make up for a missing dose on previous days. It is recommended to press only on one end of the capsule to remove it from the blister thereby reducing the risk of capsule deformation or breakage. *For details please refer to section 1.3.1 in eCTD*
	<u>Proposed (if applicable):</u> Not applicable.
Pharmaceutical form(s) and strengths	<u>Current:</u> 1 mg pomalidomide hard capsules 2 mg pomalidomide hard capsules 3 mg pomalidomide hard capsules 4 mg pomalidomide hard capsules
	<u>Proposed (if applicable):</u> Not applicable.

Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety Specification

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

Not applicable for generic products as per Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2) effective since 31 March 2017.

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

Not applicable for generic products as per Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2) effective since 31 March 2017.

Part II: Module SIII - Clinical trial exposure

Not applicable for generic products as per Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2) effective since 31 March 2017.

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

Not applicable for generic products as per Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2) effective since 31 March 2017.

Part II: Module SV - Post-authorisation experience

Not applicable for generic products as per Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2) effective since 31 March 2017.

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

Potential for misuse for illegal purposes
Not applicable for generic products as per Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2) effective since 31 March 2017.

Part II: Module SVII - Identified and potential risks

Not applicable for generic products as per Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2) effective since 31 March 2017.
Safety concerns are harmonised with reference medicinal product **Imnovid** (https://www.ema.europa.eu/en/medicines/human/EPAR/imnovid, last updated: 06/11/2023).

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Teratogenicity • Severe infection due to neutropenia and pancytopenia • Thrombocytopenia and bleeding • Cardiac failure • Non-melanoma skin cancer
Important potential risks	• Other second primary malignancies • Cardiac arrhythmia
Missing information	• None

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities as described in Zentiva Pharmacovigilance System Master File and respective quality documents are in accordance with EU Good Pharmacovigilance Practices. In addition to expedited reporting, Zentiva vigilantly undertakes follow-up activities.

- **Analysis of Adverse Drug Reactions of Special Interest**

Emerging potential safety signals can be detected by medical evaluation of ADRs as qualitative signal detection and also when evaluating cumulative aggregate data, i.e. quantitative signal detection (disproportionate reporting of adverse events). This is performed in line with Zentiva quality documents in respect with Good Pharmacovigilance Practice (GVP VI and GVP IX).
In addition, data regarding pregnancy exposure to pomalidomide are targeted for review and medically assessed in detail. These data include all pregnancy case reports collected during the specified period together with cumulative data. Non-medically confirmed case reports of suspected foetal exposure are also reviewed, whenever applicable. Non-patient exposure in pregnant females (e.g, a nurse opening the capsules, laboratory technician, or carer) is recorded in Global Safety Database and assessed during qualitative and quantitative signal detection.
Zentiva is following EURD list and its up-dates with respect to PSUR requirements.

- **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**

  - **Specific adverse reaction follow-up questionnaires:**
    - Pregnancy follow-up forms:
      - Event-Specific Questionnaire for HCP – Pregnancy Background
      - Event-Specific Questionnaire for HCP – Pregnancy Follow-up
      - Event-Specific Questionnaire for HCP – Pregnancy Outcome
      - Event-Specific Questionnaire for Primary Care Physician or Pediatrician Infant Follow-up
    - Cardiac Arrhythmia and ECG Changes
    - Cardiac Failure
    - Neutropenia
    - Second Primary Malignancies
    - Thrombocytopenia-Bleeding

For events of special interest, materials and tools (such as event-specific questions) have been developed to ensure that consistent and good quality follow-up information can be obtained.
Event-specific questionnaires are used to collect adverse reaction and follow-up information for all of the important identified and potential risks.
These forms are provided in Annex 4 of the RMP.

  - **Other forms of routine pharmacovigilance activities**

Expedited Reporting and Follow-up of Pregnancy

The pregnancy capture and follow-up procedure is detailed below.
The PPP aims to minimise the risks of teratogenicity by ensuring HCPs and patients are fully informed of and understand the risks of teratogenicity prior to starting their pomalidomide treatment. Like thalidomide and lenalidomide, pomalidomide is an immunomodulatory agent with expected teratogenic effects in humans. In order to ensure there is a consistent approach with the ability to capture all information globally, the same principles on obtaining follow-up data on pregnancies will be implemented in all territories where pomalidomide will be marketed whilst taking into account the legal and healthcare differences in those territories worldwide.

The objectives of the system are:
- To obtain information on all reported pregnancies of females exposed to pomalidomide.
- To obtain information on all reported pregnancies of female partners of male patients exposed to pomalidomide.
- To determine the root cause of all pregnancies and hence failures of the PPP.

In the EU, Zentiva will use the following method to enhance the capture of reports of pregnancy over and above reliance upon spontaneous reporting:
- Standard Initial Pregnancy Reporting Forms, which are included with each HCP Kit.
- The Educational Materials in the Educational HCP's Kit make reference to the requirement to report all suspected pregnancies to the local Zentiva office and where applicable to the NCA. The Patient Brochure also advises the patient to immediately seek medical advice if there is any risk or suspicion of possible pregnancy. Similar advice is also provided with reference to female partners of male patients.

Database of Pregnancy Reports

All reports of pregnancies received by Zentiva will be entered into Zentiva's Global Safety Database. This includes all Consumer reports in addition to HCP reports. Any abnormal pregnancy test result (eg, β-hCG elevated and positive urine pregnancy test) is immediately processed. EU Health Authorities are notified of these reports.

Follow-up

All reports of pregnancies will be followed up.
Follow-up is via the physician/obstetrician/neonatologist/paediatrician as appropriate. In each country office, any report of pregnancy is followed up by the Drug Safety staff. All reports of pregnancy are also notified to the QPPV and QPPV deputy.
All reports of abnormal pregnancy test results are followed up with the prescriber and follow-up information sent to Health Authorities.

Frequency/Duration of Follow-up

Upon receipt of a notification of pregnancy, the HCP is asked to complete the Initial Pregnancy Report Form. The Initial Pregnancy Report Form includes a field for Estimated Date of Delivery. Upon receipt of this information by Zentiva, dates for further follow-up actions are tracked. The HCP/Obstetrician is also sent a Follow-Up and Outcome Form to be completed at the outcome of the Pregnancy.
An Infant follow-up form is available for use in the event that a birth defect is detected as an outcome. Corresponding standard forms are available on request.

Root Cause of Failure of Pregnancy Prevention Programme

The Pregnancy Background Form includes questions to determine why the PPP was unsuccessful for the case in question.

Regulatory Reporting of Pregnancies

All initial pregnancy reports and follow-up information will be reported on an expedited basis within 15 days.

Compliance with the PPP will be monitored in each member state. Examples of methods to monitor compliance include keeping a record of counselling patients prior to prescription, a record of a negative pregnancy test within 3 days of prescription and a record of dispensing within 7 days of the prescription date, etc. The maximum interval of consecutive PPP compliance studies will be agreed on between Zentiva and individual NCAs.

III.2 Additional pharmacovigilance activities

Pregnancy Prevention Programme Implementation
The pregnancy capture and follow-up procedure is detailed above.
Physicians are encouraged or required as by local legislation to report pregnancies to Zentiva or in accordance to local legislation to the NCA.
Additional monitoring of the implementation of the Zentiva PPP will be carried out on a country basis in agreement with relevant NCA.

Pregnancy Prevention Programme Implementation	
Study short name and title:	Monitoring of PPP implementation.
Rationale and study objectives:	Monitoring of implementation of PPP on a country-specific basis.
Study design:	Additional monitoring of implementation of Zentiva PPP on a country-specific basis in accordance with local legal framework and with agreement of the relevant NCA (see Annex 6). Methods are anticipated to be similar to the activities in place for the reference medicinal product.
Study population:	Patients in the EU receiving pomalidomide.
Milestones:	Planned. Data will be collected, evaluated and reported as agreed with local NCAs after product launch. EURD list is respected for PSUR requirements.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
Monitoring of PPP implementation Planned	To monitor the implementation of the PPP on a country-specific basis.	Teratogenicity	Data will be collected on a regular basis after product launch and results will be reported in PSURs in accordance with the PSUR schedule.	In accordance with the PSUR schedule.

Part IV: Plans for Post-authorisation Efficacy Studies

Not applicable.

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

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product. The core requirements of the PPP, other additional risk minimisation measures and controlled access apply across all Member States, however, the local implementation may differ between Member States taking into account the local differences in healthcare delivery, legal framework, and culture. Therefore, consultations will take place with NCAs to determine the appropriate method of delivery of the PPP, other additional risk minimisation measures, and controlled access system in each Member State.

V.1. Routine Risk Minimisation Measures

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

Safety concern	Routine risk minimisation activities
Teratogenicity	Routine risk communication: The risk of teratogenicity is discussed in Section 4.8 of the SmPC. The PL warns of the potential teratogenic effects of pomalidomide and the need to avoid pregnancy. Routine risk minimisation activities recommending specific clinical measures to address the risk: Pomalidomide is contraindicated in pregnant women and in women of childbearing potential, unless all the conditions of the PPP are met. Pomalidomide is also contraindicated in male patients unable to follow or comply with the required contraceptive measures (SmPC Section 4.3). Stringent controls are required to ensure exposure of an unborn child to pomalidomide does not occur (SmPC Section 4.4). These include: • Counselling • Contraception • Pregnancy testing • Precautions for men • Additional precautions • Prescription duration Further information is provided in Sections 4.6 and 5.3 of the SmPC. Other routine risk minimisation measures beyond the Product Information: Pomalidomide is subject to restricted medical prescription.
Severe infection due to neutropenia and pancytopenia	Routine risk communication: Neutropenia, pancytopenia, and infections and infestations are listed as ADRs and neutropenia and infection are discussed in Section 4.8 of the SmPC. The PL warns that pomalidomide may cause a fall in the number of RBCs, WBCs, and platelets at the same time (pancytopenia), and describes possible symptoms. It also warns that if a patient has had HBV infection pomalidomide may cause the virus to become active again; therefore, the doctor is advised to check if the patient has ever had hepatitis B infection prior to pomalidomide treatment. Infections, including shingles and recurrence of hepatitis B infection, are listed as possible side effects.

	Routine risk minimisation activities recommending specific clinical measures to address the risk: Dose modification advice for neutropenia is included in Section 4.2 of the SmPC. A warning of neutropenia and advice for blood tests at baseline, weekly for the first 8 weeks and monthly thereafter, is included in Section 4.4 of the SmPC. Section 4.4 of the SmPC also provides a warning regarding HBV reactivation and advises that HBV status should be established before initiating treatment with pomalidomide. Patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy. Other routine risk minimisation measures beyond the Product Information: Pomalidomide is subject to restricted medical prescription.
Thrombocytopenia and bleeding	Routine risk communication: Thrombocytopenia, intracranial haemorrhage and gastrointestinal haemorrhage are discussed and listed as ADRs in Section 4.8 of the SmPC. The PL warns that pomalidomide may cause bleeding or bruising without a cause. This document lists bleeding within the skull, nosebleeds and bleeding from the bowels or stomach as possible side effects. Routine risk minimisation activities recommending specific clinical measures to address the risk: Dose modification advice for thrombocytopenia is included in Section 4.2 of the SmPC. A warning of thrombocytopenia and advice for blood tests at baseline, weekly for the first 8 weeks and monthly thereafter, is included in Section 4.4 of the SmPC. Advice for physicians to observe patients for signs of bleeding including epistaxes, especially with use of concomitant medicinal products known to increase the risk of bleeding, is also included. Other routine risk minimisation measures beyond the Product Information: Pomalidomide is subject to restricted medical prescription.
Cardiac failure	Routine risk communication: Cardiac failure is listed as an ADR in Section 4.8 of the SmPC. A warning regarding heart failure is included in the PL. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.4 of the SmPC provides warnings and precautions regarding treating patients with cardiac risk factors, and advice regarding periodic monitoring for signs or symptoms of cardiac events. Other routine risk minimisation measures beyond the Product Information: Pomalidomide is subject to restricted medical prescription.
Non-melanoma skin cancer	Routine risk communication:

	BCC of the skin and SCC of the skin are listed as ADRs in Section 4.8 of the SmPC. A warning regarding BCC and SCC is included in the PL. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Section 4.4 of the SmPC provides a warning that physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated. <u>Other routine risk minimisation measures beyond the Product Information:</u> Pomalidomide is subject to restricted medical prescription.
Other second primary malignancies	<u>Routine risk communication:</u> Section 4.4 of the SmPC states that SPM have been reported in patients receiving pomalidomide. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Section 4.4 of the SmPC provides a warning that physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated. <u>Other routine risk minimisation measures beyond the Product Information:</u> Pomalidomide is subject to restricted medical prescription.
Cardiac arrhythmia	<u>Routine risk communication:</u> AF is listed as an ADR in Section 4.8 of the SmPC. AF is listed in the PL. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None proposed. <u>Other routine risk minimisation measures beyond the Product Information:</u> Pomalidomide is subject to restricted medical prescription.

V.2. Additional Risk Minimisation Measures

In line with the innovator's reference medicinal product Imnovid, the following additional risk minimization measures will be in place:

Additional risk minimisations:

<u>Pregnancy Prevention Programme (PPP)</u>

<u>Objectives:</u>
The Zentiva PPP is designed to minimise the risk of teratogenicity by:

- Ensuring that exposure of an unborn child to pomalidomide does not occur
- Ensuring early alert to the physician of any pregnancies
- Educating patients and HCPs on the safe use of pomalidomide
- Pregnancy testing and contraceptive requirements
- A system to ensure that all appropriate measures have been performed prior to the drug being dispensed
- Managing and monitoring the distribution of pomalidomide
- Follow-up on the effectiveness of the PPP
- Compliance monitoring and assessment (examples include record of counselling patients prior to prescription, record of negative pregnancy test within 3 days of prescription and record of dispensing within 7 days of prescription date).

This controlled access is designed to minimise the risk of exposure to paediatric patients or non-target populations and provide education on the risk and the necessary steps to prevent foetal exposure.

Rationale for the additional risk minimisation activity:

The MAH of the reference medicinal product is conducting a risk minimization activity in the form of pregnancy prevention programme (PPP) to minimise the risk of teratogenicity and provide education on the risk and necessary steps to prevent foetal exposure to pomalidomide. Similar activity will be conducted for Pomalidomide Zentiva.

Target audience and planned distribution path:

The target audience is HCPs who will prescribe pomalidomide and patients.

Proposed Actions

The key elements of the Zentiva PPP are:

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

The Patient Card and/or an equivalent tool is used to manage the controlled access within the national territory as agreed with the NCA.

The process should be very similar to the one used for the reference medicinal product. The national specialities will be adapted at national level with the national competent authorities as well as the implementation plan.

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

Compliance with the PPP will be monitored on an ongoing basis in each member state in agreement with the relevant NCA (e.g, record of counselling patients prior to prescription, record of a negative pregnancy test within 3 days of prescription and a record of dispensing within 7 days of the prescription date, etc).

Criteria for Success

Outcome indicator: pregnancy exposures

Additional **HCP Educational Materials**

- **Educational healthcare professional brochure**
- **Information on where to find latest SmPC**

Objectives:
Provision of information to HCPs for the risks of:
- Thrombocytopenia and bleeding
- Cardiac failure

Rationale for the additional risk minimisation activity:
The MAH of the reference medicinal product is conducting a risk minimization activity for HCPs to understand the risks specified above and the appropriate management of these risks. Similar activity will be conducted for Pomalidomide Zentiva.

Target audience and planned distribution path:
Pomalidomide HCP additional educational materials to be provided to prescribing physicians and pharmacists.
The process should be very similar to the one used for the reference medicinal product. The national specialities will be adapted at national level with the national competent authorities as well as the implementation plan.

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

Criteria for Success
No significant increase in frequency of reports in the post marketing setting as presented in the SmPC.

Additional Patient Educational Materials

- **Educational brochures for patients**

Objectives:
Provision of a Pomalidomide Patient brochure to patients for the risk of Thrombocytopenia and bleeding.

Rationale for the additional risk minimisation activity:
The MAH of the reference medicinal product is conducting a risk minimization activity in the form of Educational brochures for patients. Similar activity will be conducted for Pomalidomide Zentiva. A Pomalidomide Patient brochure will be provided as additional educational material to advise that pomalidomide may cause thrombocytopenia and the need for regular blood tests.

Target audience and planned distribution path:
The target audience is patients who are prescribed pomalidomide.
The process should be very similar to the one used for the reference medicinal product. The national specialities will be adapted at national level with the national competent authorities as well as the implementation plan.

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

Criteria for Success
No significant increase in frequency of reports in the post marketing setting as presented in the SmPC.

The reference product also has a Direct Healthcare Professional Communication (prior to launch) in place as the additional risk minimisation measure. Since no such measures are needed for the generic products, the DHPC is not included in the RMP for Pomalidomide Zentiva.

Key messages of the additional risk minimisation measures are provided in Annex 6 of the RMP.

V.3. Summary of Risk Minimisation Measures

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

To facilitate the drafting and the publication of the RMP summary, as well as to have an overview of risk management activities in the RMP, the table also includes pharmacovigilance activities.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Teratogenicity	Routine risk minimisation measures: SmPC • Contraindicated in pregnant women and in women of childbearing potential, unless all the conditions of the PPP are met. Pomalidomide is also contraindicated in male patients unable to follow or comply with the required contraceptive measures (Section 4.3). • Warnings: criteria for women of non-childbearing potential, counselling, contraception, pregnancy testing, precautions for men, additional precautions, prescription duration (Section 4.4). • Stringent controls are required to ensure exposure of an unborn child to pomalidomide does not occur (Section 4.4). These include: counselling, contraception, pregnancy testing, precautions for men, additional precautions and prescription duration. PL • The PL warns of the potential teratogenic effects of pomalidomide and the need to avoid pregnancy. Additional risk minimisation measures: Zentiva PPP • Educational Programme – Educational HCP's kit to include educational	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Expedited reporting of all pregnancies and abnormal pregnancy test results. • Pregnancy specific questionnaires for collection of detailed initial and follow-up information for pregnancies (see Annex 4). • Follow-up of abnormal pregnancy test results • Follow-up of all pregnancies until outcome is known. • Follow-up of infant until one year after delivery. • Root cause analysis of failed Zentiva PPP as part of standard follow-up. Additional pharmacovigilance activities: Evaluation of effectiveness of PPP will be agreed on with the concerned national competent authorities.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	healthcare professional brochure, educational brochures for patients, patient card, risk awareness forms, and information on where to find latest SmPC. • Therapy management – Criteria for determining women of childbearing potential, contraceptive measures and pregnancy testing for women of childbearing potential. – Advice in SmPC and educational materials. • System to ensure appropriate measures have been completed – Patient Card to document childbearing status, counselling and pregnancy testing.	
Severe infection due to neutropenia and pancytopenia	<u>Routine risk minimisation measures:</u> SmPC • Dose modification advice for neutropenia (Section 4.2). • Warning of neutropenia, and advice for blood tests at baseline, weekly for the first 8 weeks and monthly thereafter (Section 4.4). • Warning regarding HBV reactivation and advice that HBV status should be established before treatment (Section 4.4). • Neutropenia, pancytopenia and infections and infestations are listed as ADRs and neutropenia and infection are discussed in Section 4.8. PL • Advice to patients including a warning that the doctor is advised to check if the patient has ever had hepatitis B infection prior to starting pomalidomide treatment. • A warning that pomalidomide may cause a fall in the number of RBCs, WBCs, and platelets at the same time (pancytopenia), and describes possible symptoms.	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> • Event specific questionnaire for the collection of the AE and follow-up. <u>Additional pharmacovigilance activities:</u> None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None	
Thrombocytopenia and bleeding	Routine risk minimisation measures: SmPC • Dose modification advice for thrombocytopenia (Section 4.2). • Warning of thrombocytopenia, and advice for blood tests at baseline, weekly for the first 8 weeks and monthly thereafter. Advice to monitor for signs of bleeding (Section 4.4) • Thrombocytopenia, intracranial haemorrhage and gastrointestinal haemorrhage are listed as ADRs and discussed in Section 4.8. PL • The PL warns that pomalidomide may cause bleeding or bruising without a cause, and lists bleeding within the skull, nosebleeds and bleeding from the bowels or stomach as possible side effects. Additional risk minimisation measures: • Educational HCP brochure. • Educational brochure for patients.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Event specific questionnaire for the collection of the AE and follow-up. Additional pharmacovigilance activities: None
Cardiac failure	Routine risk minimisation measures: SmPC • Section 4.4 of the SmPC provides warnings and precautions regarding treating patients with cardiac risk factors, and advice regarding periodic monitoring for signs or symptoms of cardiac events. • Listed as an ADR in Section 4.8. PL • A warning regarding heart failure is included in the PL. Additional risk minimisation measures: • Educational HCP brochure.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Event specific questionnaire for the collection of the AE and follow-up. Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Non-melanoma skin cancer	Routine risk minimisation measures: SmPC • Section 4.4 contains a warning that SPM, such as NMSC, have been reported in patients receiving pomalidomide; physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated. • BCC of the skin and SCC of the skin are listed as ADRs in Section 4.8. PL • A warning regarding BCC and SCC is included in the PL. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Event specific questionnaire for the collection of the AE and follow-up. Additional pharmacovigilance activities: None
Other second primary malignancies	Routine risk minimisation measures: SmPC • Section 4.4 states that SPM have been reported in patients receiving pomalidomide, and warns that physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated. • Preclinical safety data discussed in Section 5.3. PL • A warning regarding BCC and SCC is included in the PL. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Event specific questionnaire for the collection of the AE and follow-up. Additional pharmacovigilance activities: None
Cardiac arrhythmia	Routine risk minimisation measures: SmPC • AF listed as an ADR in Section 4.8. PL • AF listed in PL. Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Event specific questionnaire for the collection of the AE and follow-up Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	None	

Part VI: Summary of the Risk Management Plan

As the safety concerns and their management are identical for all products covered by this RMP, the information in Part VI is presented only once together for all products.

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

This summary of the RMP for Pomalidomide Zentiva 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 Pomalidomide Zentiva's RMP.

I. The medicine and what it is used for

Pomalidomide Zentiva in combination with bortezomib and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide. Pomalidomide Zentiva in combination with dexamethasone is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy (see SmPC for the full indication). It contains Pomalidomide as the active substance and it is given by oral route of administration.

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

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

Important risks of Pomalidomide Zentiva, together with measures to minimise such risks and the proposed studies for learning more about Pomalidomide Zentiva's risks, are outlined below.

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

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

Together, these measures constitute routine risk minimisation measures.

In the case of Pomalidomide Zentiva, 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 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 Pomalidomide Zentiva are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Pomalidomide Zentiva. 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 • Severe infection due to neutropenia and pancytopenia • Thrombocytopenia and bleeding • Cardiac failure • Non-melanoma skin cancer
Important potential risks	• Other second primary malignancies • Cardiac arrhythmia
Missing information	• None

II.B Summary of important risks

Summary of important risk that have corresponding additional pharmacovigilance/risk minimisation activities are:

Important identified risk: Teratogenicity	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC • Contraindicated in pregnant women and in women of childbearing potential, unless all the conditions of the PPP are met. Pomalidomide is also contraindicated in male patients unable to follow or comply with the required contraceptive measures (Section 4.3). • Warnings: criteria for women of non-childbearing potential, counselling, contraception, pregnancy testing, precautions for men, additional precautions, prescription duration (Section 4.4). • Stringent controls are required to ensure exposure of an unborn child to pomalidomide does not occur (Section 4.4). These include: counselling, contraception, pregnancy testing,

	precautions for men, additional precautions and prescription duration. PL • The PL warns of the potential teratogenic effects of pomalidomide and the need to avoid pregnancy. <u>Additional risk minimisation measures:</u> Zentiva PPP • Educational Programme – Educational HCP's kit to include educational healthcare professional brochure, educational brochures for patients, patient card, risk awareness forms, and information on where to find latest SmPC. • Therapy management – Criteria for determining women of childbearing potential, contraceptive measures and pregnancy testing for women of childbearing potential. – Advice in SmPC and educational materials. • System to ensure appropriate measures have been completed – Patient Card to document childbearing status, counselling and pregnancy testing.
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Evaluation of effectiveness of PPP will be agreed on with the concerned national competent authorities.

Important identified risk: Thrombocytopenia and bleeding	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC • Dose modification advice for thrombocytopenia (Section 4.2). • Warning of thrombocytopenia, and advice for blood tests at baseline, weekly for the first 8 weeks and monthly thereafter. Advice to monitor for signs of bleeding (Section 4.4) • Thrombocytopenia, intracranial haemorrhage and gastrointestinal haemorrhage are listed as ADRs and discussed in Section 4.8. PL • The PL warns that pomalidomide may cause bleeding or bruising without a cause, and lists bleeding within the skull, nosebleeds and bleeding from the bowels or stomach as possible side effects. <u>Additional risk minimisation measures:</u>

	• Educational HCP brochure. • Educational brochure for patients.

Important identified risk: Cardiac failure	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC • Section 4.4 of the SmPC provides warnings and precautions regarding treating patients with cardiac risk factors, and advice regarding periodic monitoring for signs or symptoms of cardiac events. • Listed as an ADR in Section 4.8. PL • A warning regarding heart failure is included in the PL. <u>Additional risk minimisation measures:</u> • Educational HCP brochure.

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Pomalidomide Zentiva.

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

There are no studies required for Pomalidomide Zentiva.

Annex 4 - Specific adverse drug reaction follow-up forms

Table of contents

POMALIDOMIDE

Specific adverse reaction/event Follow-up Form

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

Global database ID:

Country of occurrence:

Reporter Information			
Reporter (contact information):			
Obstetrician Information (Please provide)			
Obstetrician (contact information):			
Patient Information			
PATIENT initials:	PATIENT AGE:	ETHNICITY: ☐ WHITE ☐ BLACK ☐ ASIAN ☐ OTHER, SPECIFY:	
Partner of Patient Information ☐ Not applicable			
AGE:	ETHNICITY: ☐ WHITE ☐ BLACK ☐ ASIAN ☐ OTHER, SPECIFY:		
Patient ZENTIVA POMALIDOMIDE treatment information: P			
LOT NO.:	EXPIRY DATE:	DOSE:	FREQUENCY:
ROUTE:	START DATE:	STOP DATE:	
INDICATION FOR USE:			
CYTOGENETIC ABNORMALITIES: ☐ NO ☐ YES, please 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 preterm births:
No. of fetal deaths:	No. of living children:	No. of abortions: Elective: Spontaneous:
Type of delivery: ☐ Vaginal ☐ C-section		
Did birth defect occur in any previous pregnancy? ☐ No ☐ Yes ☐ Unknown If yes, please specify:		

Did a stillbirth or spontaneous abortion occur in any previous pregnancy? ☐ No ☐ Yes ☐ Unknown If Yes, in what week of pregnancy did the stillbirth or spontaneous abortion occur? Week: Was there any birth defect noted? ☐ No ☐ Yes, If Yes, 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, IF YES, SPECIFY:

Family History: CONGENITAL ABNORMALITIES ☐ NO ☐ YES IF YES, SPECIFY:
If there is a family history of congenital abnormalities, was there a consultation with a geneticist? ☐ NO ☐YES IF YES, SPECIFY:
Environmental Exposure (e.g. RADIATION, CHEMICAL EXPOSURE) ☐ NO ☐ YES IF YES, SPECIFY:
Medications/Treatments (including herbal, alternative and over-the-counter medicines and dietary supplements) During Pregnancy

MEDICATION/TREATMENT	**START DATE**	**STOP DATE/ ONGOING**	**INDICATION**

Adverse Event(s) During Pregnancy

EVENT(S)	ONSET DATE	STOP DATE / ONGOING	SERIOUS		CAUSAL RELATIONSHIP TO ZENTIVA POMALIDOMIDE P	
			Y/N	SERIOUS CRITERIA*	Y/N	IF NO, WHAT MEDICATIONS, DISEASE STATES, etc, PLAYED A ROLE IN THE EVENT?

*Serious Criteria: 1) death, 2) life-threatening, 3) required inpatient hospitalization or prolongation of existing hospitalization, 4) a persistent or significant disability/incapacity, 5) a congenital anomaly/birth defect, 6) medically significant

Root Cause of Pregnancy

1. What forms of birth control was your patient using while on ZENTIVA POMALIDOMIDE 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 ZENTIVA POMALIDOMIDE?

☐ No, please proceed to Question 5

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

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

☐ Multiple times

☐ Once a week

☐ Once every 2 weeks

☐ Once a month

☐ Not at all

☐ Other, specify

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

☐ Wanted a child

☐ Partner disapproved

☐ Side effects

☐ Health concerns

☐ Inconvenient to use

☐ Other, specify

5. Please ask your patient if they received the ZENTIVA POMALIDOMIDE Patient Information (Package Leaflet).

☐ No, please proceed to Question 5.3

☐ Yes, please answer Question 5.1

5.1 Please ask your patient if they read the ZENTIVA POMALIDOMIDE Patient Information (Package 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 ZENTIVA POMALIDOMIDE Patient Information (Package Leaflet).

☐ No, please proceed to Question 5.3

☐ Yes, please proceed to Question 5.3

5.3 Please ask your patient where most of their knowledge about contraception during ZENTIVA POMALIDOMIDE use came from

☐ Physician who prescribed ZENTIVA POMALIDOMIDE

☐ Patient Brochure to the ZENTIVA POMALIDOMIDE Pregnancy Prevention Program

☐ ZENTIVA POMALIDOMIDE Patient Information (Package 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 ZENTIVA POMALIDOMIDE use

☐ No

☐ Yes

☐ Don't know

SIGNATURE OF PERSON COMPLETING THIS FORM:
DATE of FU:

Thank you for taking time to provide this information.
Your patient's welfare is important to us.

ZENTIVA

POMALIDOMIDE
Specific adverse reaction/event Follow-up Form for HCP
Event-Specific Questionnaire for HCP – Pregnancy Follow-up
(Patient or Partner of Patient)

Global database ID:

Country of occurrence:

Date (DD/MM/YYYY): **Period covered (DD/MM/YYYY) to (DD/MM/YYYY):**
Reporter Information
REPORTER (contact information):
Patient or Pregnant Partner of Male Patient initials:

Current Pregnancy		
Prenatal Tests (If any additional medical records relating to these prenatal tests are available, please attach along with this form)		
TEST	**DATE**	**RESULT**
Ultrasound		
Ultrasound		
Ultrasound		
Amniocentesis		
Maternal serum AFP		
Other Tests, Specify:		
Pregnancy Type		
☐ SINGLETON ☐ TWIN ☐ TRIPLET ☐ OTHER, SPECIFY:		

Medications/Treatments (including herbal, alternative and over-the-counter medicines and dietary supplements) During Pregnancy			
MEDICATION/TREATMENT	START DATE	STOP DATE/ ONGOING	INDICATION

Adverse Event(s) During Pregnancy						
EVENT(S)	**ONSET DATE**	**STOP DATE / ONGOING**	**SERIOUS**		**CAUSAL RELATIONSHIP TO ZENTIVA POMALIDOMIDE**	**P**
			Y/N	**SERIOUS CRITERIA***	**Y/N**	**IF NO, WHAT MEDICATIONS, DISEASE STATES, etc, PLAYED A ROLE IN THE EVENT?**

*Serious Criteria : 1) death, 2) life-threatening,3) required inpatient hospitalization or prolongation of existing hospitalization, 4) a persistent or significant disability/ incapacity, 5) a congenital anomaly/ birth defect, 6) medically significant

Date of the FU:

Signature of the patient completing the form:

Thank you for taking time to provide this information.
Your patient's welfare is important to us.

POMALIDOMIDE

Specific adverse reaction/event Follow-up Form

Event-Specific Questionnaire for HCP – Pregnancy Outcome

Global database ID:

Country of occurrence:

Reporter Information	
REPORTER (contact information):	
Patient Information	
AGE:	ETHNICITY: ☐ WHITE ☐ BLACK ☐ ASIAN ☐ OTHER, SPECIFY:
Partner of Patient Information ☐ Not applicable	
AGE:	ETHNICITY: ☐ WHITE ☐ BLACK ☐ ASIAN ☐ OTHER, SPECIFY:
Pregnancy type: ☐ SINGLETON ☐ TWIN ☐ TRIPLE ☐ Other, please specify.	

Pregnancy Outcome			
DATE OF DELIVERY:			GESTATION AGE AT DELIVERY:
DELIVERY DETAILS	NO	YES	ADDITIONAL COMMENTS
Normal	☐	☐	
C-section	☐	☐	
Induced	☐	☐	
Assisted (e.g., forceps)	☐	☐	
Elective Termination	☐	☐	Date:
Spontaneous Abortion (≤ 20 weeks)	☐	☐	Weeks from LMP:
Fetal Death/Stillbirth (> 20 weeks)	☐	☐	
Were the Products of Conception Examined?	☐	☐	If yes, was the fetus normal? ☐ Yes ☐ No ☐ Unknown If no, please describe:

Obstetrics Information			
	NO	YES	
Complications During Pregnancy	☐	☐	If Yes, specify:
Complications During Labor/Delivery	☐	☐	If Yes, specify:
Post-partum Maternal Complications	☐	☐	If Yes, specify:
Fetal and Neonatal Status			
	NO	YES	
Live Normal Infant	☐	☐	
Fetal Distress	☐	☐	If Yes, specify:
Intra-uterine Growth Retardation	☐	☐	If Yes, specify:
Neonatal Complications*	☐	☐	If Yes, specify:
Birth Defect Noted?	☐	☐	If Yes, specify:
Sex: ☐ Male ☐ Female **Birth Weight:** lbs ___ oz ___ ***or*** kg ___ ___ ___ **Length:** inches ***or*** cm			
Apgar Score:	Unknown:	1 min:	5 mins: 10 mins:

*PLEASE PROVIDE A BRIEF SUMMARY OF THE MANAGEMENT OF THE COMPLICATIONS.

Date of the FU:

Signature of the person completing this form:

Thank you for taking time to provide this information.
Your patient's welfare is important to us.

POMALIDOMIDE

Specific adverse reaction/event Follow-up Form

Event-Specific Questionnaire for Primary Care Physician or Pediatrician – Infant Follow-up

Global database ID:

Country of occurrence:

Date of Assessment (DD/MM/YYYY):		
Age in months:		
Weight (at the time of this assessment):	lbs oz	or kg
Length (at the time of this assessment):	inches	or cm
Initials of the patient on ZENTIVA POMALIDOMIDE:		
Initials of the infant (if known):		

Please provide information for the period from (DD/MM/YYYY): to (DD/MM/YYYY):

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 ZENTIVA POMALIDOMIDE THERAPY?** (Y/N/UNKNOWN)	**FACTORS THAT MAY HAVE CONTRIBUTED TO THIS OUTCOME:** (e.g. FAMILY HISTORY, MATERNAL AGE, OBESITY, ALCOHOL CONSUMPTION DURING PREGNANCY, etc.)	**DEFECT/ ANOMALY NOTED PRIOR TO BIRTH?** (Y/N)	**INFANT AGE WHEN DEFECT/ ANOMALY WAS NOTED** (SPECIFY WEEKS OR MONTHS)

Developmental Assessment:

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

If **No**, please define your concerns regarding any developmental issues or abnormalities:

Diagnosis date of any developmental date (DD/MM/YYYY):

Infant Illnesses, Hospitalizations, Drug Therapies:

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

Signature of the person completing the form:

Date (DD/MM/YYYY):

Thank you for taking time to provide this information.
Your patient's welfare is important to us.

POMALIDOMIDE

Specific adverse reaction/event Follow-up Form

Adverse Event Report Questionnaire

Cardiac Arrhythmia and ECG Changes

Global database ID:

Country of occurrence:

INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:

Patient Demographics:	
Patient's age: or age group (if age is not available): ☐ Neonate: 0 - 27 days ☐ Infant: 28 days to 23 months ☐ Child: 2 years to 11years ☐ Adolescent: 12 years to 18 years ☐ Adult: More than 18 years and less than or equal to 65 years ☐ Elderly: equal or greater than 66 years	Gender: ☐ Male ☐ Female
Race/Ethnicity: ☐ White ☐ Black ☐ Asian ☐ Other, please specify:	

Suspect Products: Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events:

	Suspect product #1	Suspect product #2	Suspect product #3
Product name			

Daily dose and regimen			
Route of administration			
Indication			
Start date or treatment duration (DD-MM-YYYY)			
Stop date (DD-MM-YYYY)			
Lot/Batch number(s)			
Expiration date(s)			
Action taken with the suspect product*			

*Choose from one of the following for action taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown

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

	Adverse event #1:	Adverse event #2:	Adverse event #3:	Adverse event #4:
Add diagnosis here:				
Start date (DD/MM/YYYY):				
Stop date (DD/MM/YYYY):				
Time lag if AE occurred after cessation of treatment with the suspect product(s):				
Required Hospitalization				

(Yes/No)				
Life-Threatening (Yes/No)				
Persistent or significant disability (Yes/No)				
Congenital abnormality (Yes/No)				
Cause of Death (Yes/No)				
Treatment of Adverse Event				
Outcome (recovery and sequelae, if any)				
Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No)				
Did the event recur after reintroducing (Yes/No)				

Please summarize course of reported events including signs and symptoms in chronological order:

Diagnostic tests (use additional pages if needed): Please indicate test unit where applicable.

Date:	Test name:	Pre-treatment value:	AE onset value:	AE resolution value:	Normal low:	Normal high:
	CPK					
	CPK-MB					
	Troponin					
	RBC					

	Hemoglobin					
	Metabolic Panel (specify)					
	Serum potassium					
	Serum magnesium					
	Phosphorus					
	Calcium					
	Uric acid					
	Creatinine					
	BUN					

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

Concomitant Medications (use additional pages if needed):

Did the Patient take any concomitant medication?
☐ Yes (please complete below)
☐ No
☐ Unknown
Please include any antiemetics.

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

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

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

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

Additional questions:

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

Please specify the type of arrhythmia/ECG change.

Clinical signs and symptoms, if present (if none please state):
Start date (DD/MM/YYYY):
Stop date (DD/MM/YYYY):

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

Does this patient have a history of cardiac risk factors (e.g. hypertension, hyperlipidemia, hypercholesterolemia, diabetes, sepsis, obesity, smoking, renal disease, cardio respiratory problems)? If

yes, please specify below. If no, please state.

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

Test name	Pre-treatment results	AE onset results	AE resolution results
EKG findings			
Echocardiogram			
Chest X-ray			
Holter, Stress test			

Please describe specific treatments and interventions of the arrhythmia:

Date of the FU:
HCP signature:

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

Thank you for taking time to provide this information.
Your patient's welfare is important to us.

POMALIDOMIDE

Specific adverse reaction/event Follow-up Form

Adverse Event Report Questionnaire

Cardiac Failure

Global database ID:

Country of occurrence:

INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:

Patient Demographics:	
Patient's age: or age group (if age is not available): ☐ Neonate: 0 - 27 days ☐ Infant: 28 days to 23 months ☐ Child: 2 years to 11years ☐ Adolescent: 12 years to 18 years ☐ Adult: More than 18 years and less than or equal to 65 years ☐ Elderly: equal or greater than 66 years	Gender: ☐ Male ☐ Female
Race/Ethnicity: ☐ White ☐ Black ☐ Asian ☐ Other, please specify:	

Suspect Products: Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events:

	Suspect product #1	Suspect product #2	Suspect product #3
Product name			

Daily dose and regimen			
Route of administration			
Indication			
Start date or treatment duration (DD-MM-YYYY)			
Stop date (DD-MM-YYYY)			
Lot/Batch number(s)			
Expiration date(s)			
Action taken with the suspect product*			

*Choose from one of the following for action taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown

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

	Adverse event #1:	Adverse event #2:	Adverse event #3:	Adverse event #4:
Add diagnosis here:				
Start date (DD/MM/YYYY):				
Stop date (DD/MM/YYYY):				
Time lag if AE occurred after cessation of treatment with the suspect product(s):				

Required Hospitalization (Yes/No)				
Life-Threatening (Yes/No)				
Persistent or significant disability (Yes/No)				
Congenital abnormality (Yes/No)				
Cause of Death (Yes/No)				
Treatment of Adverse Event				
Outcome (recovery and sequelae, if any)				
Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No)				
Did the event recur after reintroducing (Yes/No)				

Please summarize course of reported events including signs and symptoms in chronological order:

Diagnostic tests (use additional pages if needed): Please indicate test unit where applicable.

Date:	Test name:	Pre-treatment value:	AE onset value:	AE resolution value:	Normal low:	Normal high:
	Calcium					
	Magnesium					
	Total CPK					

	CK-MB					
	Troponins					
	BNP					
	WBC					
	RBC					
	Platelets					
	Hemoglobin					
	Hematocrit					

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

Concomitant Medications (use additional pages if needed):

Did the Patient take any concomitant medication?
☐ Yes (please complete below)
☐ No
☐ Unknown

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

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

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

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

Additional questions:

Did the cardiac failure occur prior to therapy?
☐ Yes
☐ No

If the cardiac failure occurred prior to therapy, would you consider it an exacerbation?
☐ Yes
☐ No

Please provide the date the exacerbation was diagnosed (DD/MM/YYYY):

Please circle classification of cardiac failure:

a) Class I (mild) Patients with cardiac disease but without limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or angina pain
b) Class II (mild) Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina pain.
c) Class III (moderate) Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or angina pain.
d) Class IV (severe) Patients with cardiac disease resulting in the inability to carry on any physical activity without discomfort. Symptoms of heart failure or the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

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

Did the patient receive any recent blood transfusions or IV infusions?

☐ Yes
☐ No
If yes, please specify what was transfused and provide the amount transfused with dates.

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

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

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

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

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

Date of the FU:
HCP signature:

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

Thank you for taking time to provide this information.
Your patient's welfare is important to us.

POMALIDOMIDE

Specific adverse reaction/event Follow-up Form

Adverse Event Report Questionnaire

Neutropenia

Global database ID:

Country of occurrence:

INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM

Patient Demographics:	
Patient's age: or age group (if age is not available): ☐ Neonate: 0 - 27 days ☐ Infant: 28 days to 23 months ☐ Child: 2 years to 11years ☐ Adolescent: 12 years to 18 years ☐ Adult: More than 18 years and less than or equal to 65 years ☐ Elderly: equal or greater than 66 years	Gender: ☐ Male ☐ Female
Race/Ethnicity: ☐ White ☐ Black ☐ Asian ☐ Other, please specify:	

Suspect Products: Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events:

	Suspect product #1	Suspect product #2	Suspect product #3
Product name			

Daily dose and regimen			
Route of administration			
Indication			
Start date or treatment duration (DD-MM-YYYY)			
Stop date (DD-MM-YYYY)			
Lot/Batch number(s)			
Expiration date(s)			
Action taken with the suspect product*			

*Choose from one of the following for action taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown

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

	Adverse event #1:	Adverse event #2:	Adverse event #3:	Adverse event #4:
Add diagnosis here:				
Start date (DD/MM/YYYY):				
Stop date (DD/MM/YYYY):				
Time lag if AE occurred after cessation of treatment with the suspect product(s):				

Required Hospitalization (Yes/No)				
Life-Threatening (Yes/No)				
Persistent or significant disability (Yes/No)				
Congenital abnormality (Yes/No)				
Cause of Death (Yes/No)				
Treatment of Adverse Event				
Outcome (recovery and sequelae, if any)				
Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No)				
Did the event recur after reintroducing (Yes/No)				

Please summarize course of reported events including signs and symptoms in chronological order:

Diagnostic tests (use additional pages if needed): Please indicate test unit where applicable.

Date:	Test name:	Pre-treatment value:	AE onset value:	AE resolution value:	Normal low:	Normal high:
	WBC					
	ANC					

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

Concomitant Medications (use additional pages if needed):

Did the Patient take any concomitant medication?
☐ Yes (please complete below)
☐ No
☐ Unknown

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

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

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

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

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

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

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

Please provide the stage/classification of the patient's disease at the time of the infection.

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

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

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

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

Date of the FU:
HCP signature:

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

Thank you for taking time to provide this information.
Your patient's welfare is important to us.

POMALIDOMIDE

Specific adverse reaction/event Follow-up Form

Adverse Event Report Questionnaire

Second Primary Malignancies

Global database ID:

Country of occurrence:

INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:

Patient Demographics:	
Patient's age: or age group (if age is not available): ☐ Neonate: 0 - 27 days ☐ Infant: 28 days to 23 months ☐ Child: 2 years to 11years ☐ Adolescent: 12 years to 18 years ☐ Adult: More than 18 years and less than or equal to 65 years ☐ Elderly: equal or greater than 66 years	Gender: ☐ Male ☐ Female
Race/Ethnicity: ☐ White ☐ Black ☐ Asian ☐ Other, please specify:	

Suspect Products: Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events:

	Suspect product #1	Suspect product #2	Suspect product #3
Product name			

Daily dose and regimen			
Route of administration			
Indication			
Start date or treatment duration (DD-MM-YYYY)			
Stop date (DD-MM-YYYY)			
Lot/Batch number(s)			
Expiration date(s)			
Action taken with the suspect product*			

*Choose from one of the following for action taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown

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

	Adverse event #1:	Adverse event #2:	Adverse event #3:	Adverse event #4:
Add diagnosis here:				
Start date (DD/MM/YYYY):				
Stop date (DD/MM/YYYY):				
Time lag if AE occurred after cessation of treatment with the suspect product(s):				

Required Hospitalization (Yes/No)				
Life-Threatening (Yes/No)				
Persistent or significant disability (Yes/No)				
Congenital abnormality (Yes/No)				
Cause of Death (Yes/No)				
Treatment of Adverse Event				
Outcome (recovery and sequelae, if any)				
Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No)				
Did the event recur after reintroducing (Yes/No)				

Please summarize course of reported events including signs and symptoms in chronological order:

Diagnostic tests (use additional pages if needed): Please indicate test unit where applicable.

Date:	Test name:	Pre-treatment value:	AE onset value:	AE resolution value:	Normal low:	Normal high:
	Calcium					
	Phosphate					
	Uric Acid					

	Creatinine					
	Potassium					
	LDH					
	Albumin					
	Protein					

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

Concomitant Medications (use additional pages if needed):

Did the Patient take any concomitant medication?
☐ Yes (please complete below)
☐ No
☐ Unknown
Please include drugs that are potentially nephrotoxic (NSAIDS, antibiotics) including over the counter drugs.

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

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

☐ Unknown

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

☐ Family history (please specify), including history of malignancies with estimated dates:
☐ Drug/alcohol/tobacco abuse:
☐ Other (please specify):

Additional questions:
When querying about 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 the underlying disease's diagnosis.
2. Date of first clinical symptoms of SPM.
3. Stage of the underlying disease treated with ZENTIVA POMALIDOMIDE at baseline, the end of treatment if applicable, and at the time of the event with supportive documentation if available.
4. Medical history of bone marrow transplant including dates, type, donor details, source, and conditioning regimens such as treatment with alkylating agents (i.e. Cyclophosphamide, Melphalan, etc.).
5. Environmental exposure e.g. atmospheric pollutants/toxic chemicals (pesticides, herbicides, benzene, solvents); occupation/hobbies.
6. Full SPM (*specify malignancy or diagnosis if known*) biopsy reports. If not available please provide the detailed results.

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

Hematologic Malignancies (including Lymphoma and B-cell malignancy):

- Previous chemotherapy rounds (dates, type) and /or radiotherapy (zone, duration, cumulative dose) or subsequent ones if SPM (specify malignancy or diagnosis) detected after product discontinuation
- Medical conditions that compromise the immune system – HIV/AIDS, autoimmune diseases, diseases requiring immune suppressive therapy-organ transplant
- For lymphoma: Infection with HIV, Epstein-Barr virus+++, Helicobacter pylori, hepatitis B or C, human T-lymphotrophic virus type I, Burkitt's lymphoma
- Concurrent or medical/family history of inherited syndromes with genetic changes that raise the risk of acute lymphocytic leukemia (ALL) including: Down syndrome, Klinefelter syndrome, Fanconi anemia, Bloom syndrome, Ataxia-telangiectasia, Neurofibromatosis.
- Exposure to benzene (solvent used in the rubber industry, oil refineries, chemical plants, shoe manufacturing, and gasoline-related industries, and is also present in cigarette smoke, as well as some glues, cleaning products, detergents, art supplies, and paint strippers).
- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of

time, number of cigarettes/days or pack-years, age at starting
- Exposure to high levels of radiation
- Medical history of treated hematologic malignancies or concurrent leukemias or lymphomas including: Chronic Lymphocytic Leukemia (CLL), Richter transformation, and Diffuse Large B-cell lymphoma (DLBCL) such as Hodgkin's disease and plasmablastic lymphoma.
- Relevant diagnostic test results (if available), including: biopsy, immunohistochemistry, flow cytometry, cytogenetics, reverse transcriptase polymerase chain reaction, Fluorescence in situ hybridization (FISH), and next generation sequencing

Lung Cancer:
- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting
- Pre-existing pulmonary disease
- Family history of lung cancer

Thyroid Cancer:
- Personal or family history of thyroid and/or autoimmune diseases – hypo or hyperthyroidism, goiter, benign thyroid nodules, Hashimoto's disease, Graves disease
- Family history of familial medullary thyroid cancer, multiple endocrine neoplasia and familial adenomatous polyposis
- Living in iodine deficient area
- History of radiation exposure

Breast Cancer:
- Receptor status of the tumor – ER, PR, Her2/neu
- Age at onset of menses and age of menopause
- Number of pregnancies and age at first birth
- History of breastfeeding children
- Use of oral contraceptives or hormone replacement therapy
- Obesity
- Economic status, and dietary iodine deficiency

Ovarian Cancer:
- Number of pregnancies and childbearing status
- History of hormone replacement therapy
- History of breast cancer

Uterine Cancer:
- Age at onset of menses and age of menopause
- Number of pregnancies
- Use of oral contraceptives
- Obesity

Colon Cancer:

- Family or personal history of adenomatous polyposis (FAP), Lynch syndrome (Hereditary nonpolyposis colorectal cancer)
- Diet high in red meat and animal fat, refined carbohydrates, low-fiber diet, and low overall intake of fruits and vegetables
- Obesity and sedentary habits
- Any history of inflammatory conditions of digestive tract - Chronic ulcerative colitis, Crohn's disease longer duration, greater extent of colon involvement

Anorectal Cancer:

- History of infection with human papillomavirus, HIV, chronic fistulas, irradiated anal skin, leukoplakia, lymphogranulomatoma venereum, condyloma acuminatum

Gastric Cancer:

- Diet rich in pickled vegetables, salted fish, salt, and smoked meats
- Helicobacter pylori infection
- Obesity
- Previous gastric surgery
- Pernicious anemia, adenomatous polyps, gastric ulcer
- Chronic atrophic gastritis
- Radiation exposure
- History of alcohol use/smoking

Oesophageal Cancer:

- Genetic causes - tylosis (hyperkeratosis palmaris et plantaris)
- History of alcohol use/smoking
- History of chronic or acute inflammation (e.g. GERD, Barrett's esophagus, caustic ingestion), achalasia (esophageal motility disorder)
- Human papilloma virus
- Sclerotherapy
- Plummer-Vinson syndrome (dysphagia, associated with iron deficiency anemia)

Liver cancer:

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

Pancreatic Cancer:

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

Renal Cancer (renal cell carcinoma):

- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting
- Obesity
- Hypertension
- Phenacetin-containing analgesics taken in large amounts
- History of renal transplantation
- Exposure to radiopaque dyes, asbestos, cadmium, and leather tanning and petroleum products
- Inherited von Hippel-Lindau disease (VHL) disease, Adult polycystic kidney disease, Tuberous sclerosis

Bladder Cancer:

- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting
- Industrial exposure to aromatic amines in dyes, paints, solvents, leather dust, inks, combustion products, rubber, and textiles
- Occupation - painting, driving trucks, and working with metal
- Prior spinal cord injuries with long-term indwelling catheters

Prostate Cancer:

- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting
- History of high-grade prostatic intraepithelial neoplasia (PIN)
- Genome changes-deletion of chromosome 3 and fusion of TMPRSS2 and ERG genes
- Testosterone level
- History of sexually transmitted diseases
- History of vasectomy
- History of exposure to cadmium
- History of genitor-urinary infections

Head and Neck Cancer:

- History of alcohol use/smoking
- Exposure to Human papilloma virus (HPV) or Epstein-Barr virus (EBV)
- History of poor oral hygiene and/or poor nutrition
- Exposure to asbestos, wood dust, paint fumes or chemicals
- History of Gastroesophageal reflux disease (GERD) or laryngopharyngeal reflux disease (LPRD)

Brain tumors (gliomas and meningiomas):

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

Larynx Cancer:

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

Nasal and Paranasal Sinus Cancer:

- Woodworking, any dust/flour chronic exposure
- History of Infection with human papillomavirus (HPV)
- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting

Mouth and Oropharyngeal Cancer:

- History of alcohol use/smoking
- History of poor oral hygiene
- Chronic mucosal/gum irritation / ill-fitting dentures
- Betel-Nut Chewing (Indian populations)
- History of syphilis or viral infections
- Impaired immunity – AIDS, transplant with anti-rejection drugs
- Precancerous mouth plaques – Leukoplakia or erythroplasia
- History of cancer of the aero-digestive tract

Melanoma, basal cell carcinoma, squamous cell carcinoma of skin:

- History of prolonged sun exposure (UV radiation) – severe blistering sunburns, frequent tanning, use of sunlamps and tanning booths
- History of living close to equator or at high elevation
- History of skin conditions – Dysplastic nevus, Xeroderma pigmentosum, nevoid basal cell carcinoma syndromes
- Skin type – fair (pale) skin – burns easily, freckles
- Eye color – blue, green or gray, Hair color – blond or red
- Use of medication causing sensitivity to sun – antibiotics, hormones, antidepressants,
- Immune system depression – AIDS, leukemias, etc.
- Exposure to arsenic, coal tar or creosote
- For eye localization- history of oculodermal melanocytosis or Dysplastic nevus syndrome

Date of the FU:
HCP signature:

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

Thank you for taking time to provide this information.
Your patient's welfare is important to us.

POMALIDOMIDE

Specific adverse reaction/event Follow-up Form

Adverse Event Report Questionnaire

Thrombocytopenia-Bleeding

Global database ID:

Country of occurrence:

INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:

Patient Demographics:	
Patient's age: or age group (if age is not available): ☐ Neonate: 0 - 27 days ☐ Infant: 28 days to 23 months ☐ Child: 2 years to 11years ☐ Adolescent: 12 years to 18 years ☐ Adult: More than 18 years and less than or equal to 65 years ☐ Elderly: equal or greater than 66 years	Gender: ☐ Male ☐ Female
Race/Ethnicity: ☐ White ☐ Black ☐ Asian ☐ Other, please specify:	

Suspect Products: Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events:

	Suspect product #1	Suspect product #2	Suspect product #3
Product name			

Daily dose and regimen			
Route of administration			
Indication			
Start date or treatment duration (DD-MM-YYYY)			
Stop date (DD-MM-YYYY)			
Lot/Batch number(s)			
Expiration date(s)			
Action taken with the suspect product*			

*Choose from one of the following for action taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown

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

	Adverse event #1:	Adverse event #2:	Adverse event #3:	Adverse event #4:
Add diagnosis here:				
Start date (DD/MM/YYYY):				
Stop date (DD/MM/YYYY):				
Time lag if AE occurred after cessation of treatment with the suspect product(s):				

Required Hospitalization (Yes/No)				
Life-Threatening (Yes/No)				
Persistent or significant disability (Yes/No)				
Congenital abnormality (Yes/No)				
Cause of Death (Yes/No)				
Treatment of Adverse Event				
Outcome (recovery and sequelae, if any)				
Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No)				
Did the event recur after reintroducing (Yes/No)				

Please summarize course of reported events including signs and symptoms in chronological order:

Diagnostic tests (use additional pages if needed): Please indicate test unit where applicable.

Date:	Test name:	Pre-treatment value:	AE onset value:	AE resolution value:	Normal low:	Normal high:
	Platelets					
	PT					
	aPTT					

	INR					
	ESR					
	LFTs					
	Factor VIII					
	Factor IX					

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

Concomitant Medications (use additional pages if needed):

Did the Patient take any concomitant medication?

☐ Yes (please complete below; please provide relevant concomitant medications, including thromboprophylaxis (type/dose/dates as well as corresponding lab monitoring values if applicable), and possible platelet transfusion need to prevent hemorrhagic event)

☐ No

☐ Unknown

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

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

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

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

Additional questions:
Please provide location of the bleeding/hemorrhage.

Relevant medical history:
Does the patient have:
☐ History of anemia?
☐ Was patient transfusion dependent? If yes, since when and how frequent?
☐ Episodes of Hypotension?
☐ Hypertension?
☐ Gingivorrhagia or epistaxis?
☐ Headaches?
☐ Pallor?
☐ Dyspnea?
☐ Weakness?

Please describe.
☐ History of bleeding/hemorrhage?
☐ Coagulation disorder? Please describe.

☐ Please provide date of diagnosis of underlying disease, stage at the time of diagnosis and stage of the patient's disease at the time of the event.

☐ Please include bone marrow studies / x-ray / CT scan results for the event of thrombocytopenia/bleeding/hemorrhage.

☐ What treatments were given for the thrombocytopenia/ bleeding/ hemorrhage? Please include dates/dose.

Date of the FU:
HCP signature:

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

Thank you for taking time to provide this information.
Your patient's welfare is important to us.

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

Draft key messages of the additional risk minimisation measures

1. The MAH shall agree the details of a controlled access programme with the National Competent Authorities and must implement such programme nationally to ensure that:
   - Prior to prescribing (where appropriate, and in agreement with the National Competent Authority, dispensing) all healthcare professionals who intend to prescribe (and dispense) pomalidomide are provided with an Educational Healthcare Professional's Kit containing the following:
     - Educational Healthcare Professional brochure
     - Educational brochures for patients
     - Patient card
     - Risk awareness forms
     - Information on where to find latest Summary of Product Characteristics (SmPC)
2. The MAH shall implement a pregnancy prevention programme (PPP) in each Member State. Details of the PPP should be agreed with the National Competent Authorities in each Member State and put in place prior to the launch of the medicinal product.
3. The MAH should agree the contents of the Educational Healthcare Professional's Kit with the National Competent Authority in each Member State prior to launch of the medicinal product and ensure that the materials contain the key elements as described below.
4. The MAH should agree on the implementation of the controlled access programme in each Member State.

Key elements to be included

The Educational Healthcare Professional's Kit

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

Educational Healthcare Professional brochure

- Brief background on pomalidomide
- Maximum duration of treatment prescribed
  - 4 weeks for women with childbearing potential
  - 12 weeks for men and women without childbearing potential
- The need to avoid foetal exposure due to teratogenicity of pomalidomide in animals and the expected teratogenic effect of pomalidomide in humans
- Guidance on handling the blister or capsule of Pomalidomide Zentiva for healthcare professionals and caregivers
- Obligations of the health care professionals who intend to prescribe or dispense pomalidomide
  - Need to provide comprehensive advice and counselling to patients
  - That patients should be capable of complying with the requirements for the safe use of pomalidomide

- Need to provide patients with appropriate patient educational brochure and patient card and/or equivalent tool

- Safety advice relevant to all patients
  - Description and management of thrombocytopenia including incidence rates from clinical studies
  - Description and management of cardiac failure
  - Local country specific arrangements for a prescription for pomalidomide 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 pomalidomide

- Description of the PPP and categorisation of patients based on sex and childbearing potential
  - Algorithm for implementation of PPP
  - Definition of women of childbearing potential (WCBP) and actions the prescriber should take if unsure

- Safety advice for women of childbearing potential
  - The need to avoid foetal exposure
  - Description of the PPP
  - Need for effective contraception (even if the woman has amenorrhoea) and definition of effective contraception
  - That if she needs to change or stop using her method of contraception she should inform:
    - The physician prescribing her contraception that she is on pomalidomide
    - The physician prescribing pomalidomide 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 pomalidomide 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 pomalidomide 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 pomalidomide treatment
  - That if his partner becomes pregnant whilst he is taking pomalidomide or shortly after he has stopped taking pomalidomide he should inform his treating doctor immediately

- Requirements in the event of pregnancy
    - Instructions to stop pomalidomide immediately upon suspicion of pregnancy, if female patient
    - Need to refer patient to physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
    - Local contact details for reporting of any suspected pregnancy immediately
    - Pregnancy reporting form
- 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 pomalidomide is teratogenic in animals and is expected to be teratogenic in humans
- That pomalidomide may cause thrombocytopenia and the need for regular blood tests
- Description of the patient card and its necessity
- Guidance on handling pomalidomide for patients, caregivers and family members
- National or other applicable specific arrangements for a prescription for pomalidomide to be dispensed
- That the patient must not give pomalidomide to any other person
- That the patient should not donate blood during treatment (including during dose interruptions) and for at least 7 days after discontinuation of pomalidomide treatment
- That the patient should tell their doctor about any adverse events
- That any unused capsules should be returned to the pharmacist at the end of the treatment

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

Brochure for women patients with childbearing potential

- The need to avoid foetal exposure
- Description of the PPP
- The need for effective contraception and definition of effective contraception
- That if she needs to change or stop using her method of contraception she should inform:
    - The physician prescribing her contraception that she is on pomalidomide
    - The physician prescribing pomalidomide 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 pomalidomide 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 and not using effective contraception (even if the man has had vasectomy)
    - During pomalidomide treatment (including dose interruptions)
    - For at least 7 days following final dose
- That if his partner becomes pregnant, he should inform his treating doctor immediately
- That he should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of pomalidomide treatment

Patient Card or equivalent tool

The patient card shall contain the following elements:

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

Risk Awareness Forms

There should be 3 types of risk awareness forms:

- Women of childbearing potential
- Women of non-childbearing potential
- Male patient

All risk awareness forms should contain the following elements:
- teratogenicity warning
- patients receive the appropriate counselling prior to treatment initiation
- affirmation of patient understanding regarding the risk of pomalidomide 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 pomalidomide. 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 pomalidomide
    - that she understands the need to avoid pomalidomide 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 pomalidomide
  - the physician prescribing pomalidomide 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 pomalidomide 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 pomalidomide
- 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 pomalidomide
- 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 pomalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a WCBP not on effective contraception (even if the man has had a vasectomy)
- that if his partner becomes pregnant, he should inform his treating doctor immediately and always use a condom
- that he should not share the medicinal product with any other person
- that he should not donate blood or semen during treatment (including during dose interruptions) and for at least 7 days following discontinuation of pomalidomide
- that he should return the unused capsules to the pharmacist at the end of treatment.