Risk Management Plan for

Thalidomide Lipomed 100 mg coated tablets

(Thalidomide)

RMP version to be assessed as part of this application:	
RMP Version number:	1.1
Data lock point for this RMP:	29/02/2024
Date of final sign off:	29/07/2025
Rationale for submitting an updated RMP:	EMA requested to submit a Type IB variation related to the Product Information following safety changes adopted for the originator. These safety changes included updates to section 4.4 of the SmPC and Annex IID and the tools/documents included in the Educational Healthcare Professional Kit, in order to harmonise the terminology utilised in the RMP and PI documents relating to the safety concern of teratogenicity and its risk minimisation measure of the Pregnancy Prevention Plan across the 3 IMiDs. These changes are reflected in this RMP update.
Summary of significant changes in this RMP:	The significant changes in this version of the RMP reflect the safety changes adopted for the originator as described in the rationale above (update of section 4.4 of the SmPC and Annex IID and the tools/documents included in the Educational Healthcare Professional Kit). Part V (Risk Minimisation Measures), Part VI (IIB Summary of important risks) and Annex 6 (Details of proposed additional risk minimisation activities) were updated accordingly.

Other RMP versions under evaluation:	
RMP Version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable

Details of the currently approved RMP:	
Version number:	1.0
Approved with procedure:	EMA/H/C/005715/0000
Date of approval (opinion date):	21/07/2022 (CHMP opinion date) 19/09/2022 (Commission Decision date)

QPPV name:	Dr. Michael Bernstein
QPPV signature:	

Table of Contents

List of Abbreviations

AML	Acute Myeloid Leukaemia
ATC	Anatomical Therapeutic Chemical
bFGF	basic Fibroblast Growth Factor
CHMP	Committee for Medicinal Products for Human Use
COX	Cyclooxygenase
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
GVP	Good Pharmacovigilance Practices
hCG	Human Chorionic Gonadotropin
INN	International Non-proprietary Name
MAH	Marketing Authorisation Holder
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
NCA	National Competent Authority
PL	Package Leaflet
PPP	Pregnancy Prevention Programme
PSUR	Periodic Safety Update Report
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SPM	Second Primary Malignancies
TBD	To Be Determined
VEGF	Vascular Endothelial Growth Factor

Part I: Product(s) overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Thalidomide
Pharmacotherapeutic group(s) **(ATC Code)**	Immunosuppressant (ATC code: L04AX02)
Marketing Authorisation Applicant	Lipomed GmbH
Medicinal products to which this RMP refers	Thalidomide Lipomed 100 mg coated tablets
Invented name(s) in the European Economic Area (EEA)	Thalidomide Lipomed
Marketing authorisation procedure	Centralised procedure
Brief description of the product	*Chemical class:* Thalidomide is a chemically synthesized active substance with piperidine-2,6-dione structure.
	Summary of mode of action: The primary pharmacological actions of thalidomide include anti-angiogenic and immunomodulatory/anti-inflammatory activity. The mechanisms involved in these activities of thalidomide have not been fully delineated. However, it is likely that common mechanisms may be involved in both the anti-angiogenic and immunomodulatory/anti-inflammatory effects. Proposed mechanisms for the anti-angiogenic activity of thalidomide include (1) a down-regulation of TNF-α levels; (2) down-regulation of Vascular Endothelial Growth Factor (VEGF) expression; (3) inhibition of the response to basic Fibroblast Growth Factor (bFGF) and VEGF potentially through the modulation of integrin expression and impairment of migration; (4) inhibition of endothelial cell proliferation; and (5) blocking of cyclooxygenase-2 (COX-2) induction.
	Important information about its composition: None
Hyperlink to the Product Information	Please refer to Module 1.3.1.
Indications in the EEA	Thalidomide Lipomed in combination with melphalan and prednisone is indicated as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.

Dosage in the EEA	The recommended dose of thalidomide is 200 mg orally per day. A maximum number of 12 cycles of 6 weeks (42 days) should be used.
Pharmaceutical form(s) and strength(s)	Coated tablets 100 mg
Is the product/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)

There are no differences between the safety specification for Thalidomide Lipomed 100 mg coated tablets and the reference medicinal product Thalidomide BMS 50 mg hard capsules in regard to the epidemiology of the indication(s) and target population(s). For this reason, it is not necessary to provide additional information in this module of the Risk Management Plan.

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

From a non-clinical point of view, there are no differences between the safety specification for Thalidomide Lipomed 100 mg coated tablets and the reference medicinal product Thalidomide BMS 50 mg hard capsules.

Part II: Module SIII - Clinical trial exposure

No company-sponsored/initiated clinical trials have been performed with Thalidomide Lipomed 100 mg coated tablets. For this reason, it is not necessary to provide additional information in this module of the Risk Management Plan.

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

No company-sponsored/initiated clinical trials have been performed with Thalidomide Lipomed 100 mg coated tablets. For this reason, it is not necessary to provide additional information in this module of the Risk Management Plan.

Part II: Module SV - Post-authorisation experience

Since first marketing authorisation (2006), approximately 38'597 patients have been exposed to Thalidomide Lipomed. Overall, the data derived from this marketing experience were in accordance with the safety and efficacy profiles of thalidomide described in the Summary of Product Characteristics (SmPC) for the reference medicinal product Thalidomide BMS approved in the European Union.

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

For Thalidomide Lipomed 100 mg coated tablets, no additional EU requirements for the safety specification have been identified. For this reason, it is not necessary to provide additional information in this module of the Risk Management Plan.

Part II: Module SVII - Identified and potential risks

Thalidomide Lipomed 100 mg coated tablets is a hybrid medicinal product. The legal basis for the marketing authorisation application for Thalidomide Lipomed 100 mg coated tablets is Article 10(3) of Directive 2001/83/EC (as amended). According to Chapter V.C.1.1.1 of GVP Module V – Risk management systems (Rev 2), modules SI – SVII of the Risk Management Plan are not applicable for a generic medicinal product if the reference medicinal product has a Risk Management Plan. According to Chapter V.C.1.1.3 of GVP Module V – Risk management systems (Rev 2), the required elements of the Risk Management Plan for a hybrid product are generally the same as for a generic product.

A Risk Management Plan is in place for the reference medicinal product (Thalidomide BMS50 mg hard capsules).

Indication, posology, route of administration as well as the target population are identical for Thalidomide Lipomed 100 mg coated tablets and for the reference medicinal product Thalidomide BMS50 mg hard capsules.

All safety concerns included in the Risk Management Plan for Thalidomide BMS 50 mg hard capsules are also considered to be safety concerns of Thalidomide Lipomed 100 mg coated tablets and are thus included in this Risk Management Plan. No discrepancies are known to exist in regard to the characteristics of these safety concerns between the reference medicinal product Thalidomide BMS50 mg hard capsules and Thalidomide Lipomed 100 mg coated tablets.

Pursuant to a corresponding request raised as a result of the assessment of this RMP during the initial centralized marketing approval procedure, "Medication error" (in particular, the theoretical risk of confusion with reference medicinal product, thereby potentially resulting in a higher administered dose of thalidomide) has been additionally included in the Risk Management Plan for Thalidomide Lipomed as an important potential risk. No other addition, and no re-classification or removal of safety concerns compared with the Risk Management Plan of the reference medicinal product are proposed.

The important identified risks, important potential risks and missing information published in the summary of the Risk Management Plan for Thalidomide BMS 50 mg hard capsules also apply for Thalidomide Lipomed 100 mg coated tablets. The respective list of safety concerns is given below:

<u>Important identified risks:</u>

- Teratogenicity
- Severe infections (sepsis, septic shock and viral reactivation of hepatitis B)
- Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)

Important potential risks:

- Ischaemic heart disease (including myocardial infarction)
- Other second primary malignancies (SPM)
- Hepatic disorders (hepatocellular and cholestatic liver injury)
- Off-label use
- Medication error

Missing information:

- None.

The important potential risk "Medication error" is further characterized in section SVII.3.1. In accordance with the GVP guidance for risk management plans prepared under Directive 2001/83/EC Art 10(3), there is no need to provide detailed information in this module of the Risk Management Plan on any of the other safety concerns listed above.

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

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

The risks not considered important for inclusion in the list of safety concerns for Thalidomide Lipomed 100 mg coated tablets are those of the reference medicinal product. Therefore, no detailed justification for non-inclusion of risks is provided in the present Risk Management Plan.

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

All risks considered important for inclusion in the list of safety concerns for the reference medicinal product are also considered important for inclusion in the list of safety concerns for Thalidomide Lipomed.

Important potential risk "Medication error"

Pursuant to a corresponding question raised as a result of the regulatory assessment of this RMP during the initial centralized approval procedure (Procedure number EMEA/H/C/0005715), "Medication error" is additionally included in this RMP as an important potential risk. For this RMP version, characterisation of this safety concern and the correspondingly planned risk management activities as described in Parts III and V focus specifically on the potential risk of confusing Thalidomide Lipomed 100 mg coated tablets with the already marketed BMS product (Thalidomide BMS 50 mg hard capsules), which could result in a higher administered dose of thalidomide. It is acknowledged that medication errors in general (without further specification) are a possible root cause also of other untoward outcomes listed in this RMP as safety concerns, most importantly teratogenicity due to accidental intra-uterine exposure. The risk management measures proposed for the safety concern "Teratogenicity" (i.e., pregnancy prevention programme, controlled access programme, educational materials; see Part V.2) specifically aim to prevent intra-uterine exposure. These measures are therefore not duplicated under "Medication error". At this point, no other medication errors are known or anticipated for Thalidomide Lipomed that should be considered important for inclusion in the list of safety concerns.

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

Not applicable

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important identified risk: Teratogenicity

The important identified risk of teratogenicity is described in the existing Risk Management Plan for the reference medicinal product, and also applies for Thalidomide Lipomed 100 mg coated tablets. Therefore, no detailed information is provided concerning this important identified risk in the present Risk Management Plan.

Important identified risk: Severe infections (sepsis, septic shock and viral reactivation of hepatitis B)

The important identified risk of severe infections is described in the existing Risk Management Plan for the reference medicinal product, and also applies for Thalidomide Lipomed 100 mg coated tablets. Therefore, no detailed information is provided concerning this important identified risk in the present Risk Management Plan.

Important identified risk: Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)

The important identified risk of acute myeloid leukaemia and myelodysplastic syndromes is described in the existing Risk Management Plan for the reference medicinal product, and also applies for Thalidomide Lipomed 100 mg coated tablets. Therefore, no detailed information is provided concerning this important identified risk in the present Risk Management Plan.

Important potential risk: Ischaemic heart disease (including myocardial infarction)

The important potential risk of ischaemic heart disease is described in the existing Risk Management Plan for the reference medicinal product, and also applies for Thalidomide Lipomed 100 mg coated tablets. Therefore, no detailed information is provided concerning this important potential risk in the present Risk Management Plan.

Important potential risk: Other second primary malignancies (SPM)

The important potential risk of other second primary malignancies is described in the existing Risk Management Plan for the reference medicinal product, and also applies for Thalidomide Lipomed 100 mg coated tablets. Therefore, no detailed information is provided concerning this important potential risk in the present Risk Management Plan.

Important potential risk: Hepatic disorders (hepatocellular and cholestatic liver injury)

The important potential risk of hepatic disorders is described in the existing Risk Management Plan for the reference medicinal product, and also applies for Thalidomide Lipomed 100 mg coated tablets. Therefore, no detailed information is provided concerning this important potential risk in the present Risk Management Plan.

Important potential risk: Off-label use

The important potential risk of off-label use is described in the existing Risk Management Plan for the reference medicinal product, and also applies for Thalidomide Lipomed 100 mg coated tablets. Therefore, no detailed information is provided concerning this important potential risk in the present Risk Management Plan.

Important potential risk: Medication error

Note: For this Risk Management Plan, characterisation of this safety concern focusses specifically on the potential risk of confusing the Lipomed product with the already marketed BMS product (see Section SVII.2).

MedDRA terms:

Medication errors (SMQ, narrow)

Potential mechanisms:

The reference medicinal product Thalidomide BMS contains 50 mg of active substance per dosage form (hard capsule) and has been marketed for a number of years, whereas the Lipomed product contains 100 mg of active substance per dosage form (coated tablet). Erroneous administration of the same number of unit doses of the Lipomed product instead of the BMS product would thus result in doubling of the dose of the active substance. Considering that the maximum approved dose of both products is 200 mg/day, such confusion could hypothetically result in a maximum daily dose of 400 mg thalidomide.

Evidence source(s) and strength of evidence:

This is a potential risk. To date, there have been no reports of such product confusion.

Characterisation of the risk:

In absence of any reports corroborating this potential risk, in-depth characterisation is not possible. The incidence of most toxicities of thalidomide are known to correlate with dose (Ghobrial and Rajkumar, 2003). There is however no evidence that overdosage to the extent described above might result in life-threatening complications (Ghobrial and Rajkumar, 2003; SmPC Thalidomide BMS).

Risk factors and risk groups:

Not applicable, as no data are available.

Preventability:

The different dosage form of the two products (coated tablets and hard capsules, respectively) is likely to reduce the risk for confusion with the reference medicinal product. Clear instructions to healthcare professionals and patients about the correct use of this medicine, including communication of the potential for confusion with the reference medicinal product, is considered a suitable risk minimisation measure (see Part III).

Impact on the risk-benefit balance of the product:

Because product confusion as described is unlikely to result in serious toxicity, the impact of this potential risk on the risk-benefit balance of the product is assumed to be low.

Public health impact:

In absence of quantitative data on the frequency of this currently theoretical risk, the public health impact cannot be estimated. However, considering that product confusion as described above is unlikely to result in serious toxicity, the public health impact of this potential risk is assumed to be low.

SVII.3.2 Presentation of the missing information

There is no missing information for Thalidomide Lipomed 100 mg coated tablets.

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 infections (sepsis, septic shock and viral reactivation of hepatitis B) • Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)
Important potential risks	• Ischaemic heart disease (including myocardial infarction) • Other second primary malignancies (SPM) • Hepatic disorders (hepatocellular and cholestatic liver injury) • Off-label use • Medication error
Missing information	• None

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities for Thalidomide Lipomed, including adverse reaction reporting and signal detection are conducted in accordance with Directive 2001/83/EC, Regulation (EC) No 726/2004 and EU GVP guidelines. For Thalidomide Lipomed, routine pharmacovigilance activities beyond adverse reaction reporting and signal detection will include expedited reporting and diligent, active follow-up of pregnancy cases, and specific adverse reaction follow-up questionnaires.

III.1.1 Expedited reporting and active follow-up of pregnancy cases

To enhance spontaneous reporting of any pregnancy cases that might occur despite implementation of the Thalidomide Lipomed Pregnancy Prevention Programme (PPP) described in Part V, Lipomed plans the following measures:

- In the Educational Healthcare Professional's Kit (see Part V.2), information about the obligation to report any pregnancy or adverse events to Lipomed GmbH and (where applicable) the local health authority, provision of pregnancy outcome reporting form, and provision of local contact details for reporting.
- In the Patient Brochure, advice to immediately report any suspicion of pregnancy to the treating physician. Similar advice will also be provided with reference to female partners of male patients.
- Collation of all reports of suspected or confirmed pregnancies from worldwide sources in Lipomed's pharmacovigilance database, expedited medical assessment and expedited notification of Lipomed's QPPV of all initial reports of suspected or confirmed pregnancies received, in accordance with Lipomed's routine pharmacovigilance procedures;
- Diligent, active follow-up of all reports of suspected or confirmed pregnancies (including reports suggestive for pregnancy such as reports of elevated ß-hCG) in accordance with Lipomed's routine pharmacovigilance procedures, with the aim of determining the root cause for the occurrence of pregnancy as well as pregnancy outcome. Follow-up for pregnancy outcome will be scheduled and proactively sought by Lipomed's PV staff based on the estimated delivery date;
- Expedited reporting into EudraVigilance of all reports of suspected or confirmed pregnancies as well as all follow-up information received; and
- Inclusion of all reports of (suspected) pregnancies in Lipomed's continuous monitoring/signal evaluation processes and periodic reports.
- A status report of pregnancies in patients exposed to thalidomide or female partners of male patients exposed to thalidomide is provided in each PSUR. Each PSUR includes a comprehensive analysis of case reports including the reason for the occurrence of pregnancy.

Pregnancy outcome reporting form, infant follow-up form as well as follow-up forms for the patient or male patient of pregnant partner on the pregnancy background and outcome are provided in Annex 4.

III.1.2 Specific adverse reaction follow-up questionnaires

Event-specific questionnaires are proposed for the following safety concerns:

- Teratogenicity (pregnancy report forms)
- Severe infections
- AML and MDS
- Ischaemic heart disease (including myocardial infarction)
- Other second primary malignancies
- Hepatic disorders

Upon initial reporting from any source, these questionnaires will be used to facilitate structured, comprehensive collection of information relevant to the respective condition. The corresponding forms are provided in Annex 4.

III.2 Additional pharmacovigilance activities

The additional pharmacovigilance activities described below will be implemented.

- **Additional monitoring of implementation of the Thalidomide Lipomed Pregnancy Prevention Programme (PPP)**
    - Study objectives: The objective is to monitor the implementation of the PPP (see Part V.2) on a country-specific basis.
    - Study design and population: Details will be agreed on a country-specific basis with the relevant National Competent Authority (NCA) in accordance with local legal framework. Methods are anticipated to be similar to the activities in place for the reference medicinal product.
    - Milestones: Data will be collected on a regular basis after product launch. Results will be reported in PSURs, in accordance with the PSUR schedule.
- **Monitoring of drug utilisation (demographics and indication, including off-label use)**
    - Study objectives: The objective is to understand the demographics of the target population, including the number of women of childbearing potential as well as the indications in which Thalidomide Lipomed is prescribed, in order to monitor closely any potential off-label use within the national territories.
    - Study design and population: Details will be agreed on a country-specific basis with the relevant NCA in accordance with local legal framework.
    - Milestones: Results will be reported in PSURs, in accordance with the PSUR schedule.
- **Patient materials comprehension validation**
    - Study objectives: The objective of this activity is to validate comprehension of the patient materials issued for Thalidomide Lipomed prior to launch in countries where the reference medicinal product is not marketed (if applicable).
    - Study design and population: Validation will be performed in accordance with the respective national requirements, as agreed with the NCA. National patients' organisations will be involved where possible. Patients involved will be preferably

naïve to the history of thalidomide. Results of the user testing will be provided to the NCA and final materials validated at a national level.

- Milestones: Results will be submitted to the respective NCA prior to launch in the concerned country, if applicable

III.3 Summary table of additional pharmacovigilance activities

Table III.3 summarises the additional pharmacovigilance activities for Thalidomide Lipomed.

Table III.3: Summary table of additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
Additional monitoring of implementation of the Thalidomide Lipomed Pregnancy Prevention Programme (PPP) Planned	Monitoring of Thalidomide Lipomed PPP implementation on a country-specific basis	Teratogenicity	Protocol submission	TBD – after agreement with respective NCA on methods and design
			Reporting of results	Periodically as of launch, in accordance with PSUR schedule
Monitoring of drug utilisation (demographics and indication) Planned	Collection of data to understand the demographics of the target population and indications for use of Thalidomide Lipomed Monitoring of off-label use	Teratogenicity Off-label use	Protocol submission	TBD – after agreement with respective NCA on methods and design
			Reporting of results	Periodically as of launch, in accordance with PSUR schedule
Patient materials comprehension validation Planned	Validation of comprehension of patient materials in countries where the reference medicinal product is not marketed (if applicable)	Teratogenicity	Reporting of results	Prior to launch in concerned countries (if applicable)

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies have been imposed for the reference medicinal product Thalidomide BMS 50 mg hard capsules, and therefore no such studies are planned or needed for Thalidomide Lipomed 100 mg coated tablets.

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

The safety information in the proposed Product Information is aligned to the reference medicinal product. Since additional risk minimisation activities are required, a complete Part V is presented in this Risk Management Plan.

V.1 Routine Risk Minimisation Measures

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

Safety concern	Routine risk minimisation activities
Important identified risks	
Teratogenicity	Routine risk communication: Section 4.3 of the SmPC contains a contraindication in pregnant women and in females of childbearing potential unless all the conditions of the PPP are met as well as a contraindication in male patients not complying with the PPP. This is also reflected in a boxed warning at the beginning of the package leaflet (PL) and in Section 2 of the PL as well as on the outer packaging. Section 4.4 of the SmPC contains warnings and precautions for use with regard to pregnancy. This is also reflected in Section 2 of the PL. Section 4.6 of the SmPC contains information on pregnancy. This is also reflected in Section 2 of the PL. Section 4.8 of the SmPC contains information about the risk of intra-uterine death or severe birth defects. This is also stated as a warning on the outer packaging. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription Limited supply (maximum 4 weeks for women of childbearing potential and 12 weeks for men and women of non-childbearing potential)

Safety concern	Routine risk minimisation activities
Important identified risks (continued)	
Severe infections (sepsis, septic shock, and viral reactivation of hepatitis B)	Routine risk communication: Section 4.4 of the SmPC contains warnings regarding severe infections and viral reactivation. This is also reflected in Section 2 of the PL (advice that the doctor should check if the patient has or has ever had a hepatitis B infection). Section 4.8 of the SmPC lists severe infections as undesirable effects. This is also reflected in Section 4 of the PL (severe blood infections). Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.4 of the SmPC contains the advice to monitor the patients for severe infections. Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription
Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)	Routine risk communication: Section 4.4 contains a warning with regard to the risk of AML and MDS and the precaution that patients should be carefully evaluated before and during treatment. This is also reflected in Section 2 of the PL. Section 4.8 of the SmPC lists AML and MDS as adverse drug reactions. This is also reflected in Section 4 of the PL (a small number of patients may develop additional types of cancer). Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription

Safety concern	Routine risk minimisation activities
Important potential risks	
Ischaemic heart disease (including myocardial infarction)	Routine risk communication: Section 4.4 of the SmPC contains a warning related to the risk factors for myocardial infarction. This is also reflected in Section 2 of the PL. Section 4.8 of the SmPC lists myocardial infarction as adverse drug reaction. This is also reflected in Section 4 of the PL (tell your doctor if you notice symptoms of heart attack/myocardial infarction). Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 of the SmPC contains an advice regarding prophylaxis for ischaemic heart disease. This is also reflected in Sections 2 and 4 of the PL. Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription
Other second primary malignancies (SPM)	Routine risk communication: Section 4.4 of the SmPC contains a warning related to the possible occurrence of second primary malignancies (such as AML and MDS). This is also reflected in Section 2 of the PL. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription

Safety concern	Routine risk minimisation activities
Important potential risks (continued)	
Hepatic disorders (hepatocellular and cholestatic liver injury)	Routine risk communication: Section 4.8 of the SmPC lists hepatic disorders as adverse drug reactions. This is also reflected in Section 4 of the PL. Routine risk minimisation activities recommending specific clinical measures to address the risk: Sections 4.2 and 4.4 of the SmPC contain the advice to closely monitor patients with severe hepatic impairment for liver function. This is also reflected in Section 2 of the PL (talk to your doctor if you have or have had injury to the liver). Section 4.4 of the SmPC contains an advice to monitor patients for liver function. Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription
Off-label use	Routine risk communication: Section 4.1 details the therapeutic indication. This is also reflected in Section 1 of the PL. Section 4.4 contains information about the measures taken to closely monitor off-label use. On the outer packaging, patients are advised to use the product only as directed by the doctor. Throughout the SmPC, the risks associated with the use of thalidomide are described and this is also reflected in the PL. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription

Medication error	Routine risk communication: Section 4.2 details the posology and includes a cautionary statement about the potential risk for confusion with other thalidomide products. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: On the outer packaging, patients are advised to use the product only as directed by the doctor. Legal status: Medicinal product subject to restricted medical prescription

V.2 Additional Risk Minimisation Measures

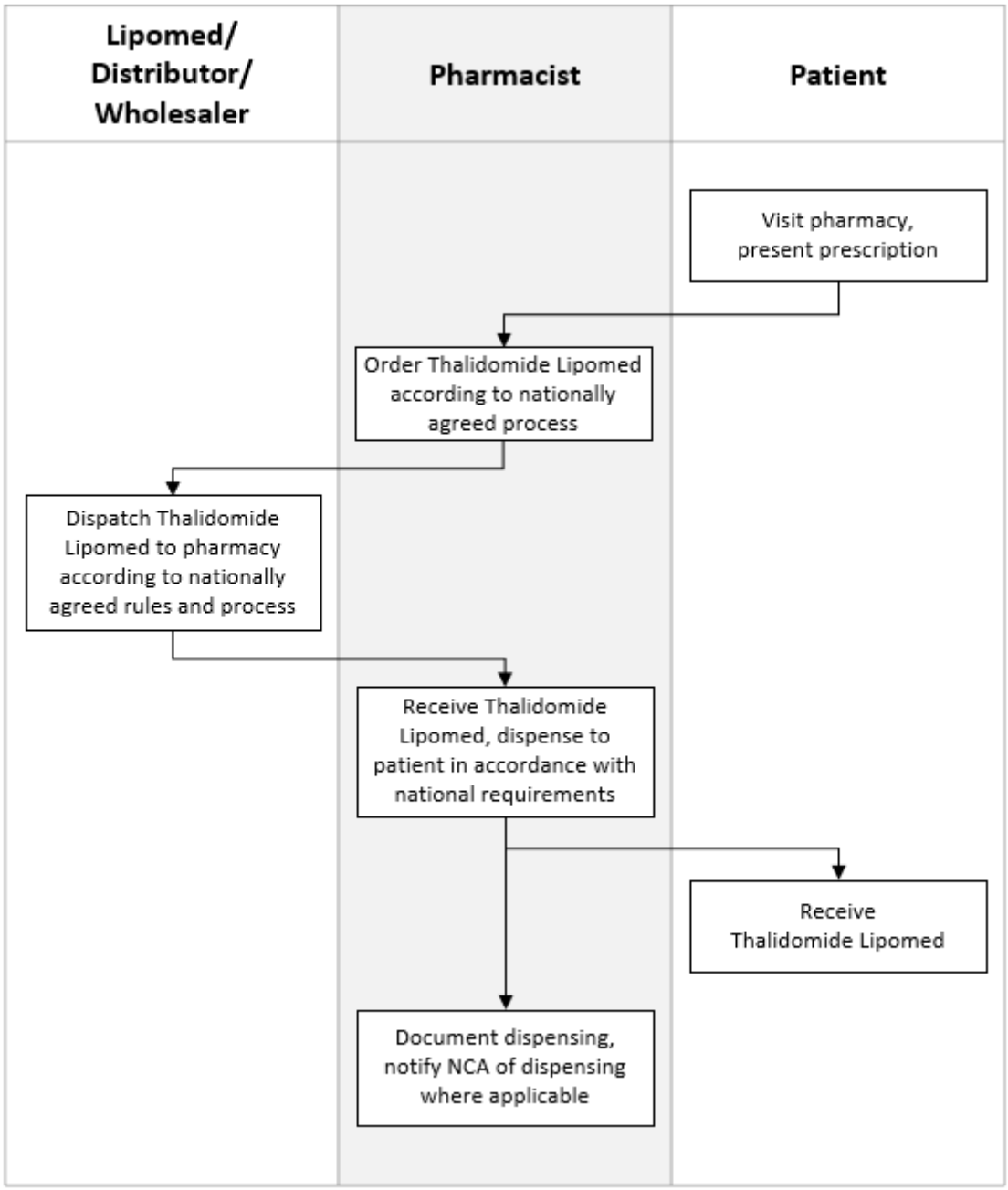
The additional risk minimisation measures for Lipomed Thalidomide will comprise:

1. Thalidomide Lipomed Pregnancy Prevention Programme (PPP); and
2. Educational materials for healthcare professionals and patients.

Both of the above measures will build upon a controlled access programme which will be put in place for Lipomed Thalidomide in each country where Thalidomide Lipomed is marketed, in agreement with the respective NCA and in accordance with local legal framework. Flowcharts of potential processes for prescribing and dispensing Thalidomide Lipomed are shown in Figure 1 and Figure 2 below. For each country where Thalidomide Lipomed will be marketed, the specific details of local implementation will be agreed with the respective NCA, before launch of Thalidomide Lipomed in that country. It is currently anticipated that the local controlled access programmes will mirror those already implemented for the reference medicinal product.

Figure 1: Flowchart of planned process for prescription of Thalidomide Lipomed

Figure 2: Flowchart of planned process for dispensing of Thalidomide Lipomed



Within the controlled access programme for Thalidomide Lipomed described above, the following additional risk minimisation measures will be implemented:

Additional Risk Minimisation 1: Thalidomide Lipomed Pregnancy Prevention Programme (PPP) with controlled access programme

Objectives:

The objective of the Thalidomide Lipomed PPP is to minimise the risk of teratogenicity by preventing intra-uterine exposure to thalidomide.

Rationale for the additional risk minimisation activity:

Thalidomide is a powerful human teratogen. Embryotic exposure is associated with a high frequency of severe and life-threatening birth defects. The sensitive period is approximately 20-36 days after fertilisation (Miller and Strömland, 1999). In view of this significant teratogenicity risk, additional measures are considered necessary to prevent exposure of an unborn child to thalidomide.

Target audience and planned distribution path:

Target audiences are physicians and pharmacists who intend to prescribe or dispense Thalidomide Lipomed, as well as patients who are to be treated with Thalidomide Lipomed.

The PPP will be implemented on a country-specific basis. Key elements of the PPP will include, in agreement with the respective NCAs:

1. Controlled access programme, as described above; and
2. Educational materials, as described below ("Additional Risk Minimisation 2: Educational Materials")

Further details of the proposed PPP are provided in Annex 6.

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

Effectiveness of the PPP will be measured on a continuous basis as follows:

- through the additional monitoring activities described in Part III ("Additional monitoring of implementation of the Thalidomide Lipomed PPP"; process indicator); and
- from the number of pregnancy reports received by Lipomed and their outcomes (outcome indicator).

Compliance with PPP requirements will be monitored and assessed. Attempts will be made to determine the root cause of any reported pregnancies and identify any potential patterns of programme failure. Data will be compared with publicly available data from the reference product. Results of effectiveness evaluation will be presented in PSURs. No formal, quantitative criteria for judging success are defined.

Additional Risk Minimisation 2: Educational Materials

Objectives:

The objective of the Educational Materials is to clearly communicate the following safety concerns of Thalidomide Lipomed together with corresponding risk minimisation requirements and recommendations:

- Teratogenicity
- Ischaemic heart disease (including myocardial infarction)
- Off-label use
- Medication error.

Rationale for the additional risk minimisation activity:

Clear communication of these important risks of thalidomide to healthcare professionals and patients will minimise their probability and/or impact.

Target audience and planned distribution path:

Target audiences are physicians and pharmacists who intend to prescribe or dispense Thalidomide Lipomed, as well as patients who are to be treated with Thalidomide Lipomed.

In agreement with the respective NCAs, the Educational Healthcare Professional's Kit will contain the following:

1. Educational Healthcare Professional brochure
2. Educational brochures for patients
3. Patient card or equivalent tool
4. Risk Awareness forms for women of childbearing potential, women of non-childbearing potential, and male patients
5. Information on where to find the latest version of the Summary of Product Characteristics (SmPC)

Further details of the proposed Educational Materials are provided in Annex 6.

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

Effectiveness of the Thalidomide Lipomed Educational Materials will be measured on a continuous basis as follows:

- through the additional monitoring activities described in Part III ("Additional monitoring of implementation of the Thalidomide Lipomed PPP" and "Monitoring of drug utilisation (demographics and indication)"; process indicators); and
- from the number and outcomes of postmarketing reports relating to the respective safety concerns received by Lipomed (outcome indicator).

Data from effectiveness evaluation will be evaluated on a regular basis. Compliance with national requirements will be monitored and assessed. Results will be presented in PSURs. No formal, quantitative criteria for judging success are defined.

V.3 Summary of risk minimisation measures

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Teratogenicity	Routine risk minimisation measures: • Routine risk communication in SmPC Sections 4.3, 4.4, 4.6 and 4.8, in PL Section 2 and in boxed warning at the beginning of the PL, on outer packaging • Restricted medical prescription only • Limited supply (maximum 4 weeks for women of childbearing potential and 12 weeks for men and women of non-childbearing potential) Additional risk minimisation measures: Thalidomide Lipomed Pregnancy Prevention Programme: • Controlled access programme • Educational Healthcare Professional's Kit (Educational Healthcare Professional brochure; Risk awareness forms for women of childbearing potential, women of non-childbearing potential, and male patients; Educational brochures for patients; Patient card or equivalent tool; Information on where to find the latest version of the Summary of Product Characteristics).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Expedited reporting and active follow-up of pregnancy cases • Specific follow-up questionnaires Additional pharmacovigilance activities: • Additional monitoring of implementation of the Thalidomide Lipomed Pregnancy Prevention Programme (PPP) – Results reported according to PSUR schedule • Monitoring of drug utilisation (demographics and indication) – Results reported according to PSUR schedule • Patient materials comprehension validation (where applicable) – Results reported to NCAs prior to launch in concerned countries

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Severe infections (sepsis, septic shock, and viral reactivation of hepatitis B)	Routine risk minimisation measures: • Routine risk communication in SmPC Sections 4.4 and 4.8, in PL Sections 2 and 4 • Recommendation for specific clinical measures in SmPC Section 4.4 • Restricted medical prescription only Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire
Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)	Routine risk minimisation measures: • Routine risk communication in SmPC Sections 4.4 and 4.8, in PL Sections 2 and 4 • Restricted medical prescription only Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire
Ischaemic heart disease (including myocardial infarction)	Routine risk minimisation measures: • Routine risk communication in SmPC Sections 4.4 and 4.8, in PL Sections 2 and 4 • Recommendation for specific clinical measures in SmPC Section 4.2, in PL Sections 2 and 4 • Restricted medical prescription only Additional risk minimisation measures: • Educational material for HCPs and patients.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire
Other second primary malignancies (SPM)	Routine risk minimisation measures: • Routine risk communication in SmPC Section 4.4, in PL Section 2 • Restricted medical prescription only Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hepatic disorders (hepatocellular and cholestatic liver injury)	Routine risk minimisation measures: • Routine risk communication in SmPC Section 4.8, in PL Section 4 • Recommendation for specific clinical measures in SmPC Sections 4.2 and 4.4, PL Section 2 • Restricted medical prescription only Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire
Off-label use	Routine risk minimisation measures: • Routine risk communication in SmPC Sections 4.1 and 4.4, in PL Section 1, on outer packaging, description of risks associated with the use of thalidomide throughout SmPC and in PL • Restricted medical prescription only Additional risk minimisation measures: • Controlled access system Educational material for HCPs.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Monitoring of drug utilisation (demographics and indication) – Results reported according to PSUR schedule
Medication error	Routine risk minimisation measures: • Routine risk communication in SmPC Section 4.2 Additional risk minimisation measures: • Educational Healthcare Professional's Kit (Educational Healthcare Professional brochure; Information on where to find the latest version of the Summary of Product Characteristics)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Part VI: Summary of the risk management plan

Summary of risk management plan for Thalidomide Lipomed 100 mg coated tablets

(Thalidomide)

This is a summary of the risk management plan (RMP) for Thalidomide Lipomed 100 mg coated tablets. The RMP details important risks of the product and how these risks can be minimised.

The summary of product characteristics (SmPC) for Thalidomide Lipomed 100 mg coated tablets and the package leaflet give essential information to healthcare professionals and patients on how the product should be used.

This summary of the RMP for Thalidomide Lipomed 100 mg coated tablets 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 the RMP for Thalidomide Lipomed 100 mg coated tablets.

I. The medicine and what it is used for

Thalidomide Lipomed in combination with melphalan and prednisone is authorised as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy (see SmPC for the full indication). It contains thalidomide as the active substance and it is given by oral route of administration.

Further information about the evaluation of the benefits of Thalidomide Lipomed 100 mg coated tablets can be found in the EPAR for Thalidomide Lipomed, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/thalidomide-lipomed

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

Important risks of Thalidomide Lipomed 100 mg coated tablets, together with measures to minimise such risks and the proposed studies for learning more about the products' 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 (PL) 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 Thalidomide Lipomed 100 mg coated tablets, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

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

II.A List of important risks and missing information

Important risks of Thalidomide Lipomed 100 mg coated tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Thalidomide Lipomed 100 mg coated tablets. 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 infections (sepsis, septic shock and viral reactivation of hepatitis B) • Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)
Important potential risks	• Ischaemic heart disease (including myocardial infarction) • Other second primary malignancies (SPM) • Hepatic disorders (hepatocellular and cholestatic liver injury) • Off-label use • Medication error
Missing information	• None

II.B Summary of important risks

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

Information related to the important identified risks and to the important potential risks is given in the tables below.

Important identified risk: Teratogenicity	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> • Routine risk communication in SmPC (including recommendations for specific clinical measures) and PL: o SmPC Section 4.3 states that thalidomide is contraindicated in pregnant women and in females of childbearing potential unless all the conditions of the Pregnancy Prevention Plan (PPP) are met, and in male patients who are unable to follow or comply with the required contraceptive measures o SmPC Section 4.4 informs about the teratogenic effects of thalidomide, provides criteria to determine whether or not a woman is of non-childbearing potential, informs about the counselling requirements for women of child-bearing potential as well as male patients, informs about effective methods of contraception, pregnancy testing, prescribing and dispensing restrictions and other precautionary measures that should be taken to minimise this risk o SmPC Section 4.6 reiterates the teratogenicity risk of thalidomide, the corresponding contraindications and the need for effective contraception o SmPC Section 4.8 reiterates the teratogenicity risk and corresponding contraindications o Corresponding risk communication in PL Section 2 and in boxed warning at the beginning of the PL, on outer packaging • Restricted medical prescription only • Limited supply (maximum 4 weeks for women of childbearing potential and 12 weeks for men and women of non-childbearing potential) <u>Additional risk minimisation measures:</u> Thalidomide Lipomed Pregnancy Prevention Programme (PPP): • Controlled access programme • Educational Healthcare Professional's Kit (Educational Healthcare Professional brochure; Educational brochures for patients; Patient card or equivalent tool; Risk awareness forms; Information on where to find latest version of the Summary of Product Characteristics).

Additional pharmacovigilance activities	• Additional monitoring of implementation of the Thalidomide Lipomed Pregnancy Prevention Programme (PPP) • Monitoring of drug utilisation (demographics and indication) • Patient materials comprehension validation (where applicable) See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Severe infections (sepsis, septic shock and viral reactivation of hepatitis B)	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC (including recommendations for specific clinical measures) and PL: o SmPC Section 4.4 contains warnings regarding severe infections and viral reactivation and recommends that patients should be monitored for severe infections including sepsis and septic shock as well as viral reactivation o SmPC Section 4.8 lists severe infections, viral infections and viral reactivation as undesirable effects o Corresponding risk communication in PL Sections 2 and 4 • Restricted medical prescription only Additional risk minimisation measures: • None

Important identified risk: Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC and PL: o SmPC Section 4.4 contains a warning with regard to the risk of AML and MDS and the precaution that patients should be carefully evaluated before and during treatment o SmPC Section 4.8 lists AML and MDS as adverse drug reactions o Corresponding risk communication in PL Sections 2 and 4 • Restricted medical prescription only Additional risk minimisation measures: • None

Important potential risk: Ischaemic heart disease (including myocardial infarction)	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC (including recommendations for specific clinical measures) and PL: o SmPC Section 4.2 contains an advice regarding prophylactic antithrombotic treatment o SmPC Section 4.4 informs about this risk and recommends action to minimise all modifiable risk factors for myocardial infarction o SmPC Section 4.8 lists myocardial infarction as adverse drug reaction o Corresponding risk communication in PL Sections 2 and 4 • Restricted medical prescription only Additional risk minimisation measures: • Educational material for HCPs and patients.

Important potential risk: Other second primary malignancies (SPM)	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC and PL: o SmPC Section 4.4 contains a warning related to the possible occurrence of second primary malignancies o Corresponding risk communication in PL Section 2 • Restricted medical prescription only Additional risk minimisation measures: • None

Important potential risk: Hepatic disorders (hepatocellular and cholestatic liver injury)	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC (including recommendations for specific clinical measures) and PL: o SmPC Section 4.2 advises to closely monitor patients with severe hepatic impairment for liver function o SmPC Section 4.4 informs about this risk and advises to monitor patients for liver function o SmPC Section 4.8 lists hepatic disorders as an undesirable effect o Corresponding risk communication in PL Sections 2 and 4 • Restricted medical prescription only Additional risk minimisation measures: • None

Important potential risk: Off-label use	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC and PL: o SmPC Section 4.1 clearly defines the therapeutic indications of this medicine o SmPC Section 4.4 informs that the implemented national controlled access programmes include collecting of data relating to the indication in order to monitor any off-label use o In PL Section 1, on outer packaging, patients are advised to use the product only as directed by the doctor • Restricted medical prescription only Additional risk minimisation measures: • Controlled access programme • Educational material for HCPs.
Additional pharmacovigilance activities	• Monitoring of drug utilisation (demographics and indication) See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Medication error	
Risk minimisation measures	Routine risk minimisation measures: • Routine risk communication in SmPC: o SmPC Section 4.2 informs that this medicine contains 100 mg of thalidomide whereas other available thalidomide-containing medicinal products contain 50 mg of thalidomide only, that this must be taken into account for the posology, that these other thalidomide products should be used if patients require less than a full 100mg dose, and that the patient must be instructed accordingly Additional risk minimisation measures: • Educational Healthcare Professional's Kit (Educational Healthcare Professional brochure; Information on where to find the latest version of the Summary of Product Characteristics)

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 Thalidomide Lipomed 100 mg coated tablets.

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

1. **Additional monitoring of implementation of the Thalidomide Lipomed Pregnancy Prevention Programme (PPP)**

   The purpose of this activity is to monitor implementation of the Thalidomide Lipomed Pregnancy Prevention Programme on a country-specific basis, as agreed with the respective national regulatory authority.

2. **Monitoring of drug utilisation (demographics and indication)**

   The purpose of this activity is to collect data to help to understand the demographics of the target population (including the number of women with childbearing potential) and indications for use of Thalidomide Lipomed, and to monitor for potential off-label use of this medicine.

3. **Patient materials comprehension validation**

   The purpose of this activity is to validate comprehension of patient materials in countries where the reference medicinal product is not marketed (if applicable).

Part VII: Annexes

Annex 4 Specific adverse drug reaction follow-up forms

Important Identified or Potential Risk	Follow-up Form Title
Teratogenicity	• Event-Specific Questionnaire for HCP: Thalidomide Lipomed Pregnancy exposure – Outcome report • Event-Specific Questionnaire for Patient or Male Patient of Pregnant Partner - PREGNANCY BACKGROUND • Event-Specific Questionnaire for Patient or Male Patient of Pregnant Partner - PREGNANCY OUTCOME • Event-Specific Questionnaire for Primary Care Physician or Paediatrician - Infant Follow- up
Severe infections (sepsis, septic shock, and viral reactivation of hepatitis B)	• Work Aid: Target Questions for Follow-up on Infections, including opportunistic infection
Acute myeloid leukaemia and myelodysplastic syndromes	• Work aid: Target Questions for Follow-up on AML or MDS in Non-MDS Indication
Ischaemic heart disease (including myocardial infarction)	• Work Aid: Target Questions for Follow-up on Myocardial Infarction
Other second primary malignancies	• Work Aid: Target Questions for Follow-up on Second Primary Malignancies
Hepatic disorders (hepatocellular and cholestatic liver injury)	• Work Aid: Target Questions for Follow-up on Hepatobiliary Disorders (hepatitis, hepatic failure, hepatotoxicity)

Teratogenicity – Pregnancy report form for HCP

This form must be returned to Lipomed GmbH, Hegenheimer Strasse 2, 79576 Weil am Rhein, Germany
Phone +49 7621 1693 472, Fax: +49 7621 1693 474, save@lipomed.com

Thalidomide Lipomed

Pregnancy exposure form – Outcome report

Female patient data

Initials: |_____|_____|_____| Date of birth: |____|____|_____| Age: |____|

For clinical trials enter

Trial ID: _____

Site number: _____ Patient number: _____

Type of exposure

Female patient: ☐Yes ☐No Female partner of male patient: ☐Yes ☐No

Exposure of a pregnant female – not patient or partner: ☐Yes ☐No

Outcome of pregnancy

Is the newborn alive? ☐No ☐Yes if no, please specify: _____

Spontaneous abortion: ☐No ☐Yes Date: |___|___|_____| Term: _____ WA histopathology: ☐No ☐Yes

Malformation: ☐No ☐Yes Details: _____

Elective abortion: ☐No ☐Yes Date: |___|___|_____| Term: _____ WA histopathology: ☐No ☐Yes

Malformation: ☐No ☐Yes Details: _____

Reason for abortion (i. e. personal, medical, malformation diagnosis in foetus…): _____

In utero death: ☐No ☐Yes Date: |___|___|_____| Term: _____ WA histopathology: ☐No ☐Yes

Malformation: ☐No ☐Yes Details: _____

Possible explanation (specify): _____

Ectopic pregnancy: ☐No ☐Yes

Delivery (to be completed only if the newborn is alive)

Date: |___|___|_____| Term: _____ WA

Mode of delivery: ☐Normal ☐Induced ☐Caesarean

Foetal distress: ☐No ☐Yes ☐Chronic ☐Acute

Normal placenta: ☐No ☐Yes ☐Unknown

Comments: _____

_____

_____

_____

Newborn condition

Sex: ☐F ☐M Weight (g): _____ Height (cm): _____ HC: _____

Premature: ☐No ☐Yes Dysmature: ☐No ☐Yes Apgar: _____ 1 min __ 5 min__

Thalidomide Lipomed | Pregnancy exposure form – Outcome report Page 1/2

This form must be returned to Lipomed GmbH, Hegenheimer Strasse 2, 79576 Weil am Rhein, Germany
Phone +49 7621 1693 472, Fax: +49 7621 1693 474, save@lipomed.com

Malformation: ☐No ☐Yes Specify: _____

Neonatal pathology: ☐No ☐Yes Specify: _____

Immediate outcome: _____ Specify: _____

Breast-feeding: ☐Yes ☐No

Additional information

Course of pregnancy

Exposure(s): ☐Tobacco ___ cig/day ☐Alcohol ___ amount/day ☐Drug addiction ☐None

Specify: _____ Other: _____

Illness(es) during pregnancy: ☐High blood pressure ☐Diabetes ☐Infection ☐None

Specify: _____ Other: _____

Hospitalisation during pregnancy: ☐No ☐Yes Reasons: _____

Antenatal diagnosis: ☐No ☐Yes

Echography – dates and results: _____ (Please enclose the results of the echography)

Other specific tests – results: _____

Retarded growth in utero: ☐No ☐Yes

Thalidomide Lipomed dosing details

Indication for Thalidomide use: _____ Discontinued: ☐No ☐Yes

Therapy start date: |___|___|_____| Therapy stop date: |___|___|_____|

Daily dose: _____

☐200 mg ☐100 mg ☐Other: _____ mg Batch No. _____

Medication(s) taken during pregnancy ☐None

Drug, dosage-form, strength, route	Dose & frequency	Therapy start date:	Therapy stop date:	Indication for use of drug
_____	_____	|___|___|_____|	|___|___|_____|	_____
_____	_____	|___|___|_____|	|___|___|_____|	_____
_____	_____	|___|___|_____|	|___|___|_____|	_____
_____	_____	|___|___|_____|	|___|___|_____|	_____
_____	_____	|___|___|_____|	|___|___|_____|	_____
_____	_____	|___|___|_____|	|___|___|_____|	_____

Reporter

☐Initial report ☐Follow-up report

Name: _____

Address: _____

Country: _____ Phone: _____

Fax: _____ Email: _____

☐Physician (Speciality _____) ☐Nurse ☐Pharmacist ☐Other healthcare professional _____

Date: |___|___|_____| Signature: _____

Event-Specific Questionnaire for Patient or Male Patient of Pregnant Partner - PREGNANCY BACKGROUND

EVENT-SPECIFIC QUESTIONNAIRE
FOR PATIENT OR MALE PATIENT OF PREGNANT PARTNER
– PREGNANCY BACKGROUND

RS-F-Draft 01
Seite: 1 / 2

Telephone: +49 7621 1693 472
Fax: +49 7621 1693 47
Email: save@lipomed.com

Date: _____
Identifier of Patient or identifier of Male Patient of Partner: _____

For a better understanding of pregnancy among patients or partners of patients on THALIDOMIDE Lipomed please complete the following questions.

1. **What forms of birth control have you been using while on THALIDOMIDE Lipomed before you/your partner got pregnant? Please check all that apply.**
   - ☐ Tubal ligation
   - ☐ IUD
   - ☐ Hormonal (birth control pills, hormonal patches, injections, vaginal rings, or implants)
   - ☐ Partner's vasectomy
   - ☐ Male latex or synthetic condom
   - ☐ Diaphragm
   - ☐ Cervical cap or shield
   - ☐ Spermicide or sponge
   - ☐ Withdrawal

2. **Were you or your partner at any time during use of THALIDOMIDE Lipomed without contraception for even one day?**
   - ☐ No, please proceed to Question 5
   - ☐ Yes, please answer Question 3, Question 4, Question 5, and Question 6

3. **How often did you have unprotected sexual intercourse?**
   - ☐ Multiple times
   - ☐ Once a week
   - ☐ Once every 2 weeks
   - ☐ Once a month
   - ☐ Not at all
   - ☐ Other, specify _____

4. **Why did you or your partner interrupt or stop using contraception?**
   - ☐ Wanted a child
   - ☐ Partner disapproved
   - ☐ Side effects
   - ☐ Health concern
   - ☐ Inconvenient to use
   - ☐ Other, specify _____

EVENT-SPECIFIC QUESTIONNAIRE
FOR PATIENT OR MALE PATIENT OF PREGNANT PARTNER
– PREGNANCY BACKGROUND

5. **Did you receive the THALIDOMIDE Lipomed Medication Guide?**
   ☐ No, please proceed to Question 6
   ☐ Yes, please answer the following question

5.1 **Did you read the THALIDOMIDE Lipomed Medication Guide?**
   ☐ No, please proceed to Question 6
   ☐ Yes, please answer the following question

5.2 **Did you understand the information in the THALIDOMIDE Lipomed Medication Guide?**
   ☐ No
   ☐ Yes

6. **Where did most of your knowledge about contraception during THALIDOMIDE Lipomed use come from?**
   ☐ Physician who prescribed THALIDOMIDE Lipomed
   ☐ THALIDOMIDE Lipomed Medication Guide
   ☐ Other, specify: _____

7. **Do you feel you and/or your partner had a good understanding of the risk of pregnancy during THALIDOMIDE Lipomed use?**
   ☐ Yes
   ☐ No
   ☐ Don't know

Event-Specific Questionnaire for Patient or Male Patient of Pregnant Partner - PREGNANCY OUTCOME

EVENT-SPECIFIC QUESTIONNAIRE
FOR PATIENT OR MALE PATIENT OF PREGNANT PARTNER
– PREGNANCY OUTCOME

RS-F-Draft 01
Seite: 1 / 1

Telephone: +49 7621 1693 472
Fax: +49 7621 1693 474
Email: save@lipomed.com

Date: _____

Identifier of Patient or identifier of Male Patient of Partner: _____

For a better understanding of pregnancy among patients or partners of patients on THALIDOMIDE Lipomed please complete the following questions.

1 **Please provide the outcome of your or your partner's pregnancy**

☐ Normal baby

☐ Abnormal baby, please specify defect:

_____

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

_____

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

_____

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

This form must be returned to Lipomed GmbH, Hegenheimer Strasse 2, 79576 Weil am Rhein, Germany
Phone +49 7621 1693 472, Fax: +49 7621 1693 474, save@lipomed.com

Thalidomide Lipomed

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

Filled out by company: Please provide information for the period from Date: |__|__|____| to Date: |__|__|____|

Filled out by company: date of questing: |__|__|____|

Data of Patient or Male Patient of Partner (Mother)

Initials: |____|____|____|Date of birth: |__|__|____| Age: |__|

Weight (kg): _____ Height (cm): _____ Gender: ☐Male ☐Female

For clinical trials enter

Trial ID: _____

Site number: _____ Patient number: _____

Data of Infant (if known)

Initials: |____|____|____|Date of birth: |__|__|____| Age: |__|

Weight (kg): _____ Height (cm): _____ Gender: ☐Male ☐Female

Anomalies Diagnosed Since Initial Report

☐ None

☐ Anomalies, please specify _____

Developmental Assessment

☐ Normal _____

☐ Abnormal, specify _____

Infant Illnesses, Hospitalizations, Drug Therapies

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

This form must be returned to Lipomed GmbH, Hegenheimer Strasse 2, 79576 Weil am Rhein, Germany
Phone +49 7621 1693 472, Fax: +49 7621 1693 474, save@lipomed.com

Reporter

☐ Initial report ☐ Follow-up report

Name: _____

Address: _____

Country: _____ Phone: _____

Fax: _____ Email: _____

☐ Physician (Speciality _____) ☐Nurse ☐Pharmacist ☐Other healthcare professional _____

Date: |__|__|____| Signature: _____

Event-specific questionnaire for severe infections

WORK AID
TARGET QUESTIONS FOR FOLLOW-UP ON
INFECTION IN GENERAL (INCL. OPPORTUNISTIC INF. ABSCESS, SOFT TISSUE INFECTIONS & INCL. NECROTISING FASCIITIS)

RS-F-Draft 01
Seite: 1 / 6

INFECTION IN GENERAL

- Tailor your follow-up questions based in existing information in the case report.

- Utilize medical judgment as always in developing targeted questions. Consult a medical reviewer if in doubt.

See also specific questions targeted to opportunistic infections below.

See also specific questions targeted to necrotizing fasciitis below.

Please provide the type and source of infection:

Has the patient had a history of recurrent infection?

☐ Yes

☐ No

If yes, please explain:

Please provide the type and the stage of the patient's disease [specify] at the time of the onset of the event:

Any history of bone marrow involvement, bone marrow transplantation or radiotherapy? If so, please provide approximate dates:

Please name any underlying condition(s) that may be relevant to the reported event, e.g., stage of disease, previous history of infection, neutropenia, exposure to monoclonal antibodies:

Please indicate one or more of the following

☐ De novo infection

☐ Recurrent infection

☐ Relapse

WORK AID
TARGET QUESTIONS FOR FOLLOW-UP ON
INFECTION IN GENERAL (INCL. OPPORTUNISTIC INF. ABSCESS, SOFT TISSUE INFECTIONS & INCL. NECROTISING FASCIITIS)

If the patient was on infection prophylaxis, did he/she receive colony stimulating factors, antibiotics, etc.?

☐ Yes

☐ No

If yes, please provide type and dates:

Please provide the following lab values at baseline, onset of the event (worst), and recovery:

Test	Normal range with units	Baseline / Date (prior to Lipomed product)	Worst / Date	Recovery / Date
WBC				
ANC				

Please provide relevant culture / serology results with dates:

Please provide any additional diagnostic test results / laboratory values (Chest x-ray, CT scan, ultrasound, CBC, haemoglobin, RBC) including baseline, event onset and recovery values, with dates, for the **reported event.**

What treatments were given for the infection? Please include dates.

WORK AID
TARGET QUESTIONS FOR FOLLOW-UP ON
INFECTION IN GENERAL (INCL. OPPORTUNISTIC INF. ABSCESS, SOFT TISSUE INFECTIONS & INCL. NECROTISING FASCIITIS)

RS-F-Draft 01
Seite: 3 / 6

Opportunistic infections *(only if applicable)*

Any suspicion or evidence of the following types of infections (incomplete list):

Viral:

☐ Epstein Barr virus (EBV)

☐ Hepatitis B (HBV)

☐ Cytomegalovirus (CMV)

☐ Herpes simplex (HSV)

☐ Varicella zoster virus (VZV)

☐ Progressive multifocal leukoencephalopathy (PML)

Protozoal:

☐ Pneumocystis carinii (PCP)

☐ Toxoplasmosis

Malignancies:

☐ Kaposi sarcoma (KS)

Fungal

☐ Candidiasis

☐ Aspergillosis

☐Histoplasmosis

☐ Cryptococcosis

Bacterial

☐ Tuberculosis (TBC)

☐ Mycobacterium avium (MAI)

☐ Salmonellosis

If the answer to any of the above is yes, please indicate whether this diagnosis has been confirmed and if so, how?

In case of suspected EBV and HBV, please provide test results in the table below

Test	Baseline / Date	Worst / Date	Recovery / Date
EBV viral load (PCR)			
EBER (Epstein Barr virus encoded RNA)			
HBs Ag			
HBs Ab			
HBc Ab			
HBV DNA			
Hepatitis A			
Hepatitis C			
Hepatitis D			
Hepatitis E			
Transaminase			
Bilirubin			

Is there a history of hepatitis or does the event represent a new infection?

WORK AID
TARGET QUESTIONS FOR FOLLOW-UP ON
INFECTION IN GENERAL (INCL. OPPORTUNISTIC INF. ABSCESS, SOFT TISSUE INFECTIONS & INCL. NECROTISING FASCIITIS)

RS-F-Draft 01
Seite: 5 / 6

Soft tissue infections including necrotizing fasciitis *(only if applicable)*

Please provide the starting localisation of the soft tissue infection:

Please indicate if local precipitating event(s) causing NF has (have) been identified at the starting site of occurrence and which ones (e.g. traumatic including surgery, minor invasive procedures [e.g. joint aspirations]. and penetrating injuries [e.g., insect and animal bites) and nontraumatic including soft tissue burns):

If the suspect drug is an injectable form, please specify the route of administration = SC or IV:

If the route of administration of the suspect drug was SC, please specify if the starting localisation of the soft tissue infection was at the injection site:

Please specify if any of the below risk factor has been identified:

☐ Diabetes
☐ Chronic disease, if yes specify
☐ Immunosuppressive drugs (including corticosteroids), if yes specify:
☐ Malnutrition
☐ Age >60 years
☐ Peripheral vascular disease
☐ Alcohol /drug abuse (to specify)
☐ Renal failure
☐ Obesity
☐ Recent childbirth
☐ Recent infection with rash (e.g., varicella)
☐ Recent stay in health care facility
☐ Recent dental work
☐ Others, if yes specify

WORK AID
TARGET QUESTIONS FOR FOLLOW-UP ON
INFECTION IN GENERAL (INCL. OPPORTUNISTIC INF. ABSCESS, SOFT TISSUE INFECTIONS & INCL. NECROTISING FASCIITIS)

Please provide the identified infectious causative pathogen and source of identification (e.g., skin or blood culture / serology results with dates):

Please provide any additional diagnostic test results if available (e.g., Scan; MRI; Skin biopsy; Muscle biopsy):

Please provide additional lab data including:

Test	Normal range with units	Baseline / Date (prior to Lipomed product)	Worst / Date	Recovery / Date
CPK MM				
CPK				
lactate				
BUN				
Creatinine				
glucose				
INR				
PT				
D-Dimer				
Serum C- reactive protein				

Please provide treatment of the infection including local procedures (e.g., surgery):

Please provide post-surgery pathology results also including cultures from deep specimen samples during the intervention:

Possible leisure- or work-related activities with risk for soft tissue infections (e.g. fishing, weightlifting / heavy work-out / gardening…):

Event-specific questionnaire for AML and MDS

WORK AID
TARGET QUESTIONS FOR FOLLOW-UP ON AML OR MDS IN NON-MDS INDICATION

RS-F-Draft 01
Seite: 1 / 1

- *This Work Aid is to be used for events of MDS or AML where the therapy indication is not MDS*
- *Tailor your follow-up questions based on existing information in the case report.*
- *Utilize medical judgment as always in developing targeted questions. Consult a medical reviewer if in doubt.*

1. Please provide the date when AML or MDS was initially diagnosed with stage / classification
2. Please provide full bone marrow results as well as full cytogenetics at baseline and at the time of diagnosis of MDS or AML with dates. Please specify if this information is not available or not evaluable.
3. Please specify AML type if not included in the bone marrow or cytogenetics documents. Please specify if this information is not available or not evaluable.
4. Please also provide the stage / classification of the underlying indication (i.e. multiple myeloma) at the time of the MDS or AML diagnosis. Please specify if this information is not available or not evaluable. Is there evidence of progression of underlying disease? Please explain.
5. Please provide relevant medical history including familial history of malignancies, environmental exposure, blood transfusion dependence status.
6. Please provide information on any antineoplastic treatments the patient may have received including radiotherapy with radiation zone for any malignant neoplasm specifying the indication for this. Please provide duration of treatment with dates, and also cumulative dose if available.

Antineoplastic treatment (incl. dosage form, strength, route)	Dose & frequency	Start date	Stop date	Cumulative dose	Indication

7. Please provide all concomitant medications including indications, therapy dates and dosing information. These should include concurrent anti-myeloma therapy, colony-stimulating factors, and / or ESAs.

Concomitant drugs (incl. dosage form, strength, route)	Dose & frequency	Start date	Stop date	Indication

8. Please provide *[Lipomed drug]* dosing regimen with dates and dose.
9. Please specify what treatment was received for the AML / MDS.
10. What was the outcome of AML /MDS? If fatal outcome, please provide circumstances surrounding the death.

Event-specific questionnaire for myocardial infarction

WORK AID
TARGET QUESTIONS FOR FOLLOW-UP ON
MYOCARDIAL INFARCTION

RS-F-Draft 01
Seite: 1 / 1

- Tailor your follow-up questions based on existing information in the case report.

- Utilize medical judgment as always in developing targeted questions. Consult a medical reviewer if in doubt.

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

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

3. Please provide the following laboratory data: serial CPK and MB, troponin, BNP, Blood cell counts, hemoglobin (Hgb), hematocrit (Hct), electrolytes including Mg, and Ca. Please include baseline, worst, and recovery values and dates drawn.

Test	Normal range with units	Baseline / Date (prior to Lipomed product)	Worst / Date	Recovery / Date
CPK				
CPK-MB				
Troponin				
BNP				
Blood cell counts				
Hgb				
Hct				
Mg				
Ca				

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

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

Event-specific questionnaire for other second primary malignancies

WORK AID
TARGET QUESTIONS FOR FOLLOW-UP ON
SECOND PRIMARY MALIGNANCIES
(SPM)

RS-F-Draft 01
Seite: 1 / 5

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

- Tailor your follow-up questions based on existing information in the case report.

- Utilize medical judgment as always in developing targeted questions. Consult a medical reviewer if in doubt.

Core Questions for Follow-up of SPMs:

1. Dates of treatment with *[Lipomed product]* in regard to the event
2. Dates of the underlying disease's diagnosis
3. Stage of the underlying disease treated with *[Lipomed product]* at baseline, the end of treatment if applicable, and at the time of the event with supportive documentation if available
4. Previous history of malignancies (personal/familial) with estimated dates
5. Underlying medical history and concomitant diseases
6. 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
7. Environmental exposure e.g., atmospheric pollutants / toxic chemicals (pesticides, herbicides, benzene, solvents); occupation / hobbies
8. Tobacco, alcohol abuse?
9. Date of diagnosis of SPM (specify malignancy or diagnosis if known). Please provide date of first clinical symptoms of SPM.
10. Full SPM (specify malignancy or diagnosis if known) biopsy reports with exact stage. If not available please provide the detailed results.
11. Treatment of SPM (specify malignancy or diagnosis if known)

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

Lung Cancer:

- Smoking history - length of time, number of cigarettes / day, age at starting, gender, product smoked and depth of inhalation
- Pre-existing pulmonary disease
- Family history of lung cancer

Lymphoma:

- Medical conditions that compromise the immune system – HIV / AIDS, autoimmune diseases, diseases requiring immune suppressive therapy-organ transplant
- Infection with HIV, Epstein-Barr virus+++, Helicobacter pylori, hepatitis B or C, human T-lymphotropic virus type I, Burkitt's lymphoma

WORK AID
TARGET QUESTIONS FOR FOLLOW-UP ON
SECOND PRIMARY MALIGNANCIES
(SPM)

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

Breast Cancer:

- Receptor status of the tumor - ER, PR, Her2 or Her2/neu
- Age at onset of menses and age of menopause
- Number of pregnancies and age at first birth
- History of breastfeeding children
- Use of oral contraceptives or hormone replacement therapy
- Obesity
- Ethnic group, economic status, 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, chronic fistulas, irradiated anal skin, leukoplakia, lymphogranulomatoma venereum, condyloma acuminatum
- HIV status

WORK AID

TARGET QUESTIONS FOR FOLLOW-UP ON

SECOND PRIMARY MALIGNANCIES

(SPM)

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

Oesophageal Cancer:

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

Liver cancer:

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

Pancreatic Cancer:

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

Renal Cancer (renal cell carcinoma):

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

Bladder Cancer:

WORK AID

TARGET QUESTIONS FOR FOLLOW-UP ON

SECOND PRIMARY MALIGNANCIES

(SPM)

RS-F-Draft 01

Seite: 4 / 5

- Smoking
- Industrial exposure to aromatic amines in dyes, paints, solvents, leather dust, inks, combustion products, rubber, and textiles
- Occupation - painting, driving trucks, and working with metal
- Prior spinal cord injuries with long-term indwelling catheters

Prostate Cancer:

- Ethnic group
- 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 (NOTE: genitourinary?) infections

Head and Neck Cancer:

- Smoking and alcohol use
- Prolonged sun exposure
- Exposure to Human papilloma virus (HPV) or Epstein-Barr virus (EBV)
- Ethnic group
- History of poor oral hygiene and / or poor nutrition
- Exposure to asbestos, wood dust, paint fumes or chemicals
- History of gastroesophageal reflux disease (GERD) or laryngopharyngeal reflux disease (LPRD)

Brain tumors (gliomas and meningiomas):

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

Larynx Cancer:

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

Nasal and Paranasal Sinus Cancer:

- Woodworking, any dust / flour chronic exposure

WORK AID
TARGET QUESTIONS FOR FOLLOW-UP ON
SECOND PRIMARY MALIGNANCIES
(SPM)

- History of infection with human papillomavirus (HPV)
- Smoking

Mouth and Oropharyngeal Cancer:

- Smoking
- Alcohol use
- 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:

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

Event-specific questionnaire for hepatic disorders

WORK AID

Target Questions for Follow-up on HEPATOBILIARY DISORDERS (Hepatitis, Hepatic Failure, Hepatotoxicity)

RS-F-Draft 01

Seite: 1 / 2

- Tailor your follow-up questions based in existing information in the case report.

- Utilize medical judgment as always in developing targeted questions. Consult a medical reviewer if in doubt.

1. Did the patient have a history of liver disease, hepatitis, alcohol, or substance abuse? Please include the onset dates of disease.

2. Did the patient have any of the following pre-existing diseases: cardiac disease, congestive heart failure, or infections?

3. What clinical signs and symptoms (with dates) were observed? Jaundice, bleeding, encephalopathy?

4. Did the patient receive other chemotherapies simultaneously with the *<Lipomed product(s)>*?

☐ Yes ☐ No

a. If yes, please provide drug name, dosing, and therapy dates.

Drug name	Dose	Start date	End date

5. Did the patient receive other chemotherapies prior to taking *<Lipomed product(s)>*?

☐ Yes ☐ No

a. If yes, please provide drug name, dosing, and therapy dates.

Drug name	Dose	Start date	End date

6. Was there any concurrent use of potentially hepatotoxic drugs or products?

WORK AID

Target Questions for Follow-up on HEPATOBILIARY DISORDERS (Hepatitis, Hepatic Failure, Hepatotoxicity)

RS-F-Draft 01

Seite: 2 / 2

☐ Yes ☐ No

a. If yes, please provide drug name, dosing, and therapy dates.

Drug name	Dose	Start date	End date

7. Please provide the treatment / intervention received due to the events.

8. Please include the following laboratory values including baseline, worst (onset value), and recovery values. (Include dates collected)

Laboratory test	Baseline	Worst (event onset)	Recovery
CBC			
Metabolic panel			
Coagulation panel			
Liver function tests			
AST			
Alk			
ALT			
Phos			
LDH			
Bilirubin			
Viral hepatitis serology			

9. Please provide the results of the following diagnostics (include dates completed)

- Liver biopsy:
- CT scans:
- MRI:
- Ultrasound:

Annex 6 Details of proposed additional risk minimisation activities

- **Additional risk minimisation measures**

1. The MAH shall agree the details of a controlled access programme with the National Competent Authorities in each Member State where Thalidomide Lipomed is marketed 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) Thalidomide Lipomed 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.
5. Prior to approval by the National Competent Authority and launch of the medicinal product in countries where the reference product is not approved or marketed, the MAH should ensure that the educational materials are provided to and reviewed by the national patients' organisations or if such an organisation does not exist or can not be involved, by a relevant patients' group. Patients involved should be preferably naïve to the history of thalidomide. Results of the user testing will have to be provided to the National Competent Authority and final materials validated at a national level.
6. The MAH should also agree with each Member State prior to launch of the medicinal product:
   - The most appropriate strategies to monitor the off-label use within national territories
   - The collection of detailed data to understand demographics of target population, indication and number of women of childbearing potential in order to monitor the off-label use within national territory.
7. The MAH shall notify the EMA and the appropriate national patients and victims representatives of the proposed launch date before launch in each Member State.

Key elements to be included

Educational Healthcare Professional's Kit

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

Educational Healthcare Professional brochure

- History and background of thalidomide
- Maximum duration of treatment prescribed
  - 4 weeks for women with childbearing potential
  - 12 weeks for men and women without childbearing potential
- Teratogenicity and the need to avoid foetal exposure
- Guidance on handling the blister or coated tablet of Thalidomide Lipomed for healthcare professionals and caregivers

- Obligations of the healthcare professionals who intend to prescribe or dispense Thalidomide Lipomed
    - Need to provide comprehensive advice and counselling to patients
    - That patients should be capable of complying with the requirements for the safe use of Thalidomide Lipomed
    - Need to provide patients with the appropriate patient educational brochure, patient card and/or equivalent tool
- Safety advice relevant to all patients
    - Guidance to prevent medication errors (potential confusion with the reference medicinal product)
    - Description and management of ischaemic heart disease (including myocardial infarction)
    - Local country specific arrangements for a prescription for thalidomide to be dispensed
    - That any unused coated tablets 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 Thalidomide Lipomed
- 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 thalidomide
        - The physician prescribing thalidomide 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 Thalidomide Lipomed 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 Thalidomide Lipomed 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 Thalidomide Lipomed treatment
    - That if his partner becomes pregnant whilst he is taking Thalidomide Lipomed or shortly after he has stopped taking Thalidomide Lipomed he should inform his treating doctor immediately

- Requirements in the event of pregnancy
    - Instructions to stop Thalidomide Lipomed immediately upon suspicion of pregnancy, if female patient
    - Need to refer patient to physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
    - Local contact details for reporting of any suspected pregnancy immediately
- Local contact details for reporting adverse reactions

Educational Brochures for patients

The Educational brochures for patients should be of 3 types:
- Brochure for women 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 thalidomide is teratogenic
- That thalidomide may cause ischaemic heart disease, (including myocardial infarction)
- Description of the patient card and its necessity
- Guidance on handling Thalidomide Lipomed for patients, caregivers and family members
- National or other applicable specific arrangements for a prescription for Thalidomide Lipomed to be dispensed
- That the patient must not give Thalidomide Lipomed 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 Thalidomide Lipomed treatment
- That the patient should tell their doctor about any adverse events
- That any unused coated tablets 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 thalidomide
    - The physician prescribing thalidomide 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 Thalidomide Lipomed immediately upon suspicion of pregnancy
- The need to contact their doctor immediately upon suspicion of pregnancy

Brochure for male patients
- The need to avoid foetal exposure
- The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraception (even if the man has had vasectomy)
    - During Thalidomide Lipomed 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 Thalidomide Lipomed treatment

Patient Card or equivalent tool

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

Risk Awareness Forms

There should be 3 types of risk awareness forms:
- Women of childbearing potential
- Women of non-childbearing potential
- Male patient

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