THALIDOMIDE BMS® (THALIDOMIDE)

RMP- Risk Management Plan
PPP- Pregnancy Prevention Programme

INFORMATION FOR HEALTHCARE PROFESSIONALS

BROCHURE

This brochure is intended for healthcare professionals involved in prescribing or dispensing thalidomide, and contains information about:

- **Preventing harm to unborn babies:** If Thalidomide BMS® (thalidomide) is taken during pregnancy, it can cause severe birth defects or death to an unborn baby.
- **Other side effects of thalidomide:** Ischaemic heart disease including myocardial infarction. Further information and recommended precautions can be found in the thalidomide Israeli approved Prescribing Information.
- **Thalidomide Pregnancy Prevention Programme:** This Programme is designed to prevent unborn babies being exposed to thalidomide. It will provide you with information about how to follow the programme and explain your responsibilities.

It is a requirement of the Pregnancy Prevention Programme that all healthcare professionals ensure that they have read and understood this brochure.

To ensure your patients' safety, please read this brochure carefully. You must ensure that your patients fully understand what you have told them about thalidomide before starting treatment.

CONTENTS

Introduction

Thalidomide BMS® (thalidomide) belongs to a group of medicines known as 'immunomodulatory' medicines. As the prescriber or pharmacist, you play a central role in ensuring that thalidomide is used safely and in accordance with the requirements of the Pregnancy Prevention Programme.

The Pregnancy Prevention Programme (PPP) includes the following elements: HCP brochure, HCP registration form, patient brochure, patient registration form, pharmacy registration form and pregnancy tests results report form.

Thalidomide is prescribed and dispensed according to the Thalidomide Pregnancy Prevention Programme. Please also refer to the Israeli approved Prescribing Information for further information.

When thalidomide is given in combination with other medicinal products, the corresponding Israeli approved Prescribing Information must be consulted prior to initiation of treatment.

The purpose of educating participants in the programme is to ensure that patients and healthcare providers involved in the PPP process understand how to minimise risk of foetal exposure and the resultant severe life-threatening congenital malformations.

The local educational materials contain information regarding the safety concern of teratogenicity (PPP), other relevant safety concerns and the PPP controlled distribution plan.

Thalidomide should be taken as a single dose at bedtime, to reduce the impact of somnolence. Thalidomide should be taken with water, at least one hour after food.

This brochure is part of the 'Thalidomide Pregnancy Prevention Programme' because if Thalidomide BMS® (thalidomide) is taken during pregnancy it can cause severe birth defects or death to an unborn baby. In the 1950s and 1960s, approximately 12,000 children were born with severe birth defects caused by thalidomide, and approximately 5,000 are alive today.

This brochure will describe your responsibilities as a prescriber or a pharmacist, and will summarize the information that you need to tell your patient to ensure they are aware of the risks and their responsibilities.

All of the Thalidomide Pregnancy Prevention Programme materials are contained within the 'Educational Healthcare Professional's Kit', and additional copies can be obtained by contacting Neopharm. These materials can be used for counselling patients on the risks of thalidomide and the precautions to be taken.

You must be sure that your patients fully understand what you have told them about thalidomide before starting treatment.

Special warnings and precautions for use:

Teratogenic effects. Thalidomide is a powerful human teratogen, inducing a high frequency of severe and life-threatening birth defects. Thalidomide must never be used by women who are pregnant or by women who could become pregnant unless all the conditions of the Thalidomide Pregnancy Prevention Programme are met. The conditions of the Thalidomide Pregnancy Prevention Programme must be fulfilled for all male and female patients.

Thalidomide must never be used by women who are pregnant, as just a single dose (1 capsule) can induce a high frequency of severe and life-threatening birth defects. Thalidomide must never be used by women who are able to become pregnant unless they follow the Thalidomide Pregnancy Prevention Programme. Since thalidomide may be present in the seminal fluid of male patients, male patients must also follow contraceptive measures.

Requirements in the event of a suspected pregnancy:

- Stop treatment immediately, if female patient
- Refer female patient to a physician specialized or experienced in teratology for evaluation and advice
- Notify the Israeli MoH of all suspected pregnancies in female patients or partners of male patients – please refer to "Reporting of side effects"
- Notify Neopharm by contacting the Product Safety and Quality Department – please refer to "Reporting of side effects"
- Neopharm will wish to follow-up with you on the progress of all pregnancies

Thalidomide and Other Potential Side Effects

In addition to the teratogenic effects of thalidomide, other potential side effects your patients should be aware of include ischaemic heart disease, including myocardial infarction. Please refer to the **Thalidomide Israeli approved Prescribing Information** for full information about the side effects and recommended precautions.

Your patient should be encouraged to report any unusual reactions or side effects from their medication to their prescriber. The side effects are also described in the thalidomide product information leaflet, which patients should read thoroughly.

Healthcare Professionals' Obligations

Obligations of healthcare professionals who intend to prescribe or dispense thalidomide are:

- The need to provide comprehensive advice and counselling to patients
- To ensure their patients are capable of complying with the requirements for the safe use of thalidomide
- To provide patients with the appropriate patient educational materials
- To self register and register their patients to the Pregnancy Prevention Programme
- To report any pregnancy, or adverse events to Neopharm and the Israeli MoH

Information for Prescribers

Introduction

As the prescriber, you play a central role in ensuring that thalidomide is used safely.

Most importantly, you will be helping to ensure that your patients understand the risks involved in taking thalidomide and that they are aware of their responsibilities in preventing foetal exposure to the drug. In addition, you may need to help your patients understand the processes involved in the thalidomide Pregnancy Prevention Programme.

If you refer your patient to a fertility expert (e.g., obstetrician or gynaecologist) for further contraceptive advice, it is your responsibility to ensure that the fertility expert is aware of the Thalidomide Pregnancy Prevention Programme requirements.

A summary of the Thalidomide Pregnancy Prevention Programme process is found on the last page of this brochure.

You must ensure that your patient understands the information before they complete their section of the 'Patient Registration Form'.

Please make use of the patient brochures to help explain the relevant information.

Specific advice for female patients

At treatment initiation, your female patients must be counselled on the risks of thalidomide therapy including the risk of birth defects, other side effects and important precautions associated with thalidomide therapy.

Childbearing and non–childbearing potential

In order to provide appropriate information to your female patients about the precautions they must follow when using thalidomide, it is important to determine whether your patient is or is not of childbearing potential.

Women not of childbearing potential include women who fulfil at least one of the following criteria:

- Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year (amenorrhoea following cancer therapy or during breast-feeding does not rule out childbearing potential)
- Premature ovarian failure confirmed by a specialist gynaecologist
- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner syndrome, uterine agenesis

Contraceptive methods

Women of childbearing potential must use at least one highly effective AND one additional effective barrier method of contraception for at least 4 weeks before start of treatment, during treatment, and until at least 4 weeks after thalidomide treatment and even in case of dose interruptions unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis.

If your patient is not established on effective contraception, they must be referred preferably to an appropriately trained health care professional for contraceptive advice before initiating contraception.

The following can be considered to be examples of highly effective methods of contraception:

- Intrauterine device (IUD)
- Levonorgestrel-releasing intrauterine system (IUS)
- Medroxyprogesterone acetate depot

- Tubal ligation
- Sexual intercourse with a vasectomized male partner only; vasectomy must be confirmed by two negative semen analyses
- Ovulation inhibitory progesterone-only pills (ie, desogestrel)

The following can be considered to be examples of additional effective barrier methods of contraception:

- Condom
- Diaphragm
- Cervical cap

Because of the increased risk of venous thromboembolism in patients with multiple myeloma, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception, they should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception.

If your patient needs to change or stop using her method of contraception during her thalidomide therapy, she must understand the need to inform:

- The physician prescribing her contraception about the thalidomide treatment.
- You, if a change or stop of method of contraception is needed.

Your patient should be advised that if she is a woman of childbearing potential and has heterosexual intercourse without using a method of contraception while taking thalidomide or believes for any reason that she may be pregnant, she must stop treatment immediately and inform her physician immediately.

The pregnancy report should be provided by filling-in the Pregnancy reporting form.

Pregnancy testing

For women of childbearing potential, you must perform a pregnancy test prior to issuing a prescription. A pregnancy test is required even if the patient has not had heterosexual intercourse since her last pregnancy test.

The pregnancy test must have a minimum sensitivity of 25 mIU/ml. The test must be performed by a healthcare professional, and the result must be negative before thalidomide treatment can begin or continue.

The pregnancy test must be performed during the consultation when thalidomide is being prescribed, or in the 3 days prior to the visit to the prescriber once the patient had been using effective contraception for at least 4 weeks. Further pregnancy tests must then be performed at least every 4 weeks during thalidomide treatment, and a final test conducted at least 4 weeks after treatment ends.

Specific Advice for Male Patients

Your male patients must be counselled on the risks of thalidomide therapy including the risk of birth defects, other side effects and important precautions associated with thalidomide therapy.

Patients must be informed not to donate semen or sperm during treatment (including during dose interruptions) and for at least 4 weeks following discontinuation of thalidomide.

Contraceptive methods

As thalidomide is present in seminal fluid, male patients should always use a condom during sexual intercourse with a female partner of childbearing potential**.** Condoms must be used during treatment, during dose interruption and for at least 4 weeks after treatment has finished.

Patients should be instructed that if their partner does become pregnant whilst he is taking thalidomide or within 4 weeks after he has stopped taking thalidomide, he should inform his prescriber immediately. The partner should inform her physician immediately. It is recommended that she be referred to a physician specialized in teratology for evaluation and advice.

Advice for all Patients

All patients should be advised not to donate blood during treatment (including dose interruptions) and for at least 4 weeks after cessation of treatment with thalidomide.

If they discontinue therapy or if there are any unused capsules at the end of their treatment, they must return any unused thalidomide to the pharmacist.

They must also understand that their thalidomide is only for them, and it:

- Must not be shared with anyone else, even if they have similar symptoms
- Must be stored away safely so no-one else could take the capsules by accident
- Must be kept out of reach of children

Patients should be advised that capsules should not be opened or crushed. If powder from thalidomide makes contact with the skin, the skin should be washed immediately and thoroughly with soap and water. If thalidomide makes contact with the mucous membranes, they should be thoroughly flushed with water.

Prescribing Thalidomide BMS®

Before issuing the initial prescription, you must:

- Counsel the patient on the safe use of thalidomide in accordance with the measures described in this brochure and the Israeli approved Prescribing Information
- Obtain their written confirmation (using the 'Patient Registration Form') that they have received and understood this information

Retain a copy of the written confirmation, provide a copy to the patient and send a copy to Neopharm.

Prescriptions for women of childbearing potential can be for a maximum duration of treatment of 4 weeks according to the approved indications dosing regimens, and prescriptions for all other patients can be for a maximum duration of 12 weeks. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day.

Issuing a prescription is subject to a negative pregnancy test performed within 3 days prior to registration of the prescription.

Dispensing of thalidomide should occur within a maximum of 7 days of the prescription.

For all other patients, prescriptions of thalidomide should be limited to a maximum duration of 12 consecutive weeks and continuation of treatment requires a new prescription.

- **Repeat or subsequent prescriptions:** the patient must return for every repeat prescription of thalidomide. You may prescribe a maximum of 4 weeks of therapy for women of childbearing potential, or 12 weeks of therapy for all other patients.

- **Pregnancy testing:** for women of childbearing potential, you will need to refer the patient to repeat the pregnancy test even if the patient has not had heterosexual intercourse since the last test. Further information regarding pregnancy testing is provided in the pregnancy testing section.

Information for Pharmacists

Introduction

As a pharmacist, you play an important role in ensuring that thalidomide is used safely and correctly.

Dispensing thalidomide

For women of childbearing potential, ideally pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of thalidomide should occur within a maximum of 7 days of the prescription.

Dispensing advice

- Ensure the pack is sealed; capsules must not be removed from blisters and packaged into bottles.
- For each prescription, dispense a maximum of a 4-week supply for women of childbearing potential or a 12-week supply for all other patients.
- Instruct patients to return any unused thalidomide to the pharmacy.

Patient education

At each supply of thalidomide, please ensure that you remind patients about the teratogenic risk and the safe use and handling of thalidomide.

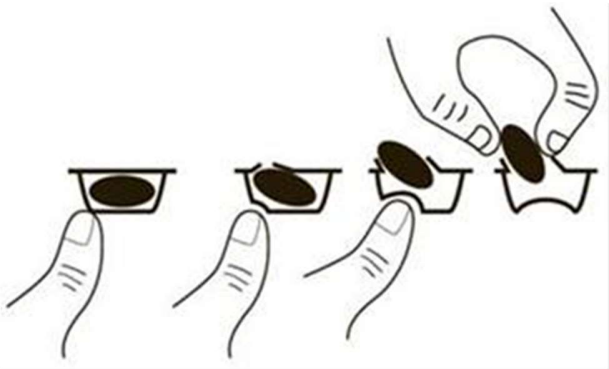
Points to consider for handling the medicinal product: for healthcare professionals and caregivers

Do not share the medicinal product with anyone else, even if they have similar symptoms. Store them safely so that no-one else can take them by accident and keep them out of the reach of children.

Keep the blisters with the capsules in the original pack.

Capsules can occasionally become damaged when pressing them out of the blister, especially when the pressure is put onto the middle of the capsule. Capsules should not be pressed out of the blister by putting pressure on the middle. The pressure should be located at one site only, which reduces the risk of the capsule deforming or breaking (see figure below).

Healthcare professionals and caregivers should wear disposable gloves when handling the blister or capsule. Remove gloves carefully to prevent skin exposure. Place in a sealable plastic polyethylene bag. Dispose of any unused medication in accordance with local regulations. Hands should then be washed thoroughly with soap and water. Women who are pregnant or suspect they may be pregnant should not handle the blister or capsule. Refer below for further guidance.



When handling the medicinal product use the following precautions to prevent potential exposure if you are a healthcare professional or caregiver

- If you are a woman who is pregnant or suspect that you may be pregnant, you should not handle the blister or capsule.
- Wear disposable gloves when handling product and/or packaging (i.e., blister or capsule).
- Use proper technique when removing gloves to prevent potential skin exposure (see below).

- Place gloves in a sealable plastic polyethylene bag and dispose them according to local requirements.
- Wash hands thoroughly with soap and water after removing gloves.
- Patients should be advised never to give the medicinal product to another person.

If a drug product package appears visibly damaged, use the following extra precautions to prevent exposure

- If outer carton is visibly damaged – **do not open**.
- If blister strips are damaged or leaking or capsules are noted to be damaged or leaking – **close outer carton immediately**.
- Place the product inside a sealable plastic polyethylene bag.
- Return unused pack to the pharmacist for safe disposal as soon as possible.

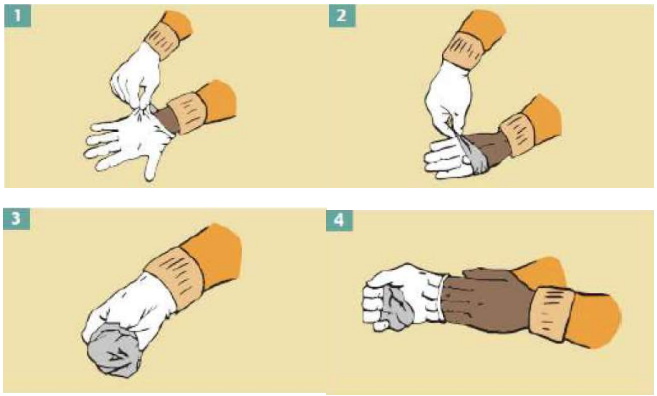
If product is released or spilled, take proper precautions to minimize exposure by using appropriate personal protection

- If capsules are crushed or broken, dust containing drug substance may be released. Avoid dispersing the powder and avoid breathing on or inhaling the powder.
- Wear disposable gloves to clean up the powder.
- Place a damp cloth or towel over the powder area to minimize entry of powder into the air. Add excess liquid to allow the material to enter solution. After handling, clean the area thoroughly with soap and water, then dry it.
- Place all contaminated materials, including damp cloth or towel, and the gloves, into a sealable polyethylene plastic bag. Dispose of it according to local requirements for medicinal products.
- Wash your hands thoroughly with soap and water after removing the gloves.
- Please report to Neopharm by email: *drugsafety@neopharmisrael.com*, or by calling 03-9373796

If the contents of the capsule are attached to the skin or mucous membranes

- If you touch the drug powder, please wash exposed area thoroughly with running water and soap.
- If drug powder makes contact with one or both of your eyes, remove and discard any contact lenses in use. Then, thoroughly flush eyes with water for at least 15 minutes. If irritation occurs, please contact an ophthalmologist.

Proper Technique for Removing Gloves



- Grasp outside edge near wrist (1).
- Peel away from hand, turning glove inside-out (2).
- Hold in opposite gloved hand (3).
- Slide ungloved finger under the wrist of the remaining glove, being careful not to touch the outside of the glove (4).
- Peel off from inside, creating a bag for both gloves.
- Discard in appropriate container.
- Wash your hands with soap and water thoroughly.

Reporting of Adverse Reactions

The safe use of thalidomide is of paramount importance. As part of Neopharm's ongoing safety monitoring, the company wishes to learn of Adverse Reactions that have occurred during the use of thalidomide. For Adverse Reactions reports, please refer to "Reporting of side effects".

Contact Details

For information and questions on the risk management of Neopharm's products, and the Pregnancy Prevention Programme, please email the Registration Holder's Product Safety and Quality Department at: drugsafety@neopharmgroup.com

The Thalidomide Pregnancy Prevention Programme at a Glance

Prescriber: You must

- Communicate the risks and benefits of thalidomide therapy to your patient.
- Complete a 'Patient Registration Form' along with your patient (this only needs to be done once). Retain a copy with your records, provide a copy to the patient and send a copy to Neopharm.
- Provide contraceptive counselling at treatment initiation.
- Refer women of childbearing potential patient to a pregnancy test up to 3 days prior to every prescription.
- Remind your patient of the safe use of thalidomide at each consultation.

Pharmacist: You must

- Remind your patient of the safe use of thalidomide, each time a prescription is dispensed.
- Comply with the Procedure for prescribing thalidomide according to the Risk Management Program / Pregnancy Prevention Program approved by the Israeli MoH.

Reporting of side effects

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment that appears on the homepage of the Ministry of Health's website (www.health.gov.il) which links to a portal, or by the following link: https://sideeffects.health.gov.il
and by emailing the Registration Holder's Product Safety and Quality Department at:
drugsafety@neopharmgroup.com
Tel: 03-9373796

Personal Data Privacy

Neopharm processes personal data relating to patients receiving this product and to health professionals involved in their therapeutic management, for the purposes of managing and reducing the risk linked to the use of this product as legally required. You may contact us at any time to ask what personal data we process about you. If such a request places Neopharm or its affiliates in breach of its obligations under applicable laws, regulations or codes of practice, then Neopharm may not be able to comply with your request. To exercise your rights: privacy@Neopharmgruop.com

Risk awareness form for counselling the patient being fully informed of/about the safe use of Thalidomide BMS® (Thalidomide)

This document was last approved in May 2025 by the Israeli Ministry of Health (MOH)

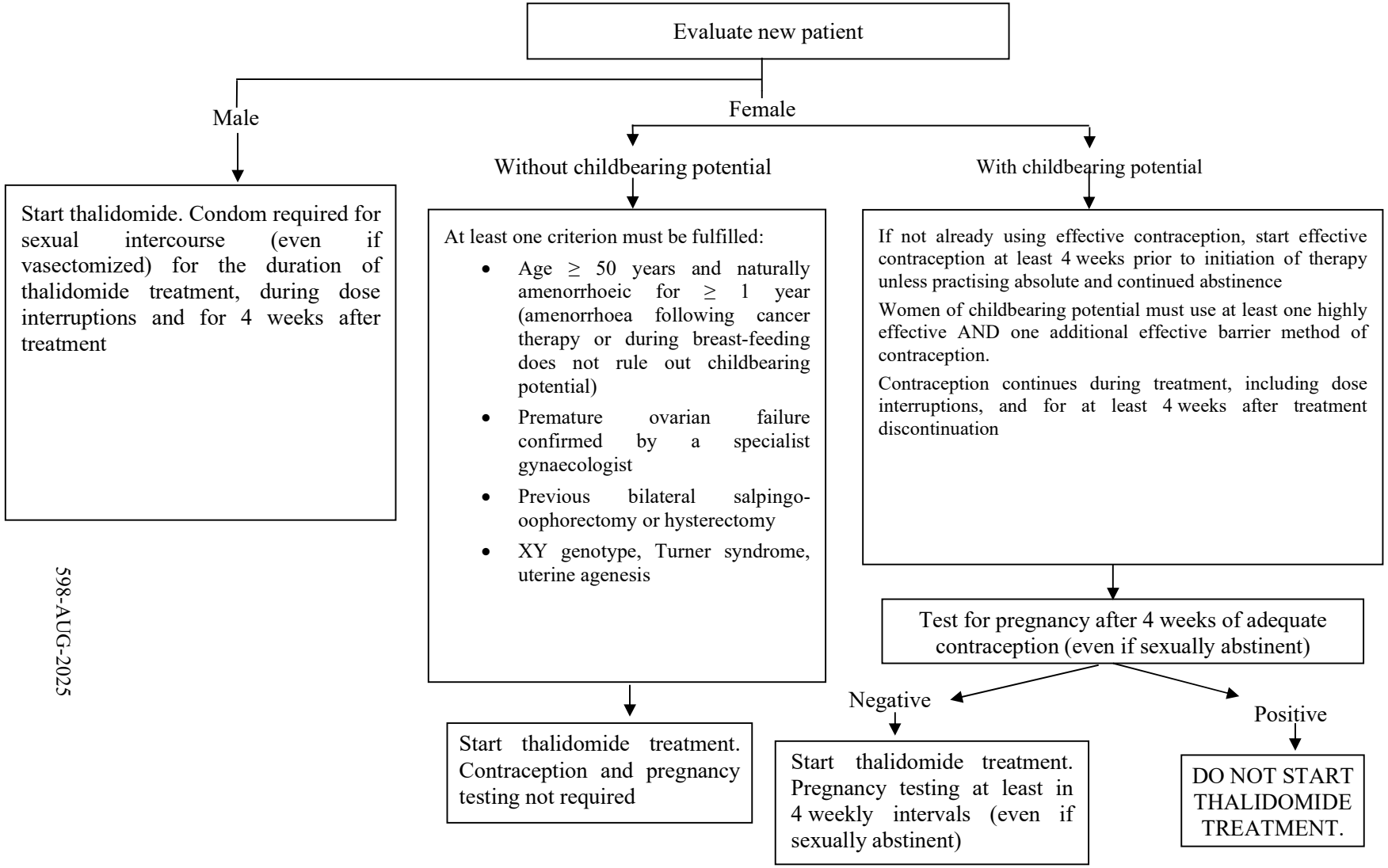
Please choose the applicable column for the risk category of the patient and refer to the counselling messages provided.

Did you inform your patient:	**Male Patients**	**Women of Non-childbearing Potential***	**Women of Childbearing Potential**
1) Thalidomide is a powerful human teratogen and the need to avoid foetal exposure		N/A	
2) That if she is pregnant or plans to be, she must not take Thalidomide	N/A	N/A	
3) That she understands the need to avoid Thalidomide during pregnancy and to use simultaneously two reliable methods of contraception (One highly effective method [(i.e. an intra-uterine device or implant) and additional effective barrier methods (i.e. condom, Diaphragm, cervical cap)] 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	N/A	N/A	
4) That if she needs to change or stop using her method of contraception she should inform: a) the physician prescribing her contraception that she is taking Thalidomide b) the physician prescribing Thalidomide that she has stopped or changed her method of contraception	N/A	N/A	
5) Of the need for pregnancy tests (i.e., before treatment) at least every 4 weeks during treatment and after treatment	N/A	N/A	
6) Of the need to stop Thalidomide immediately upon suspicion of pregnancy and the patient should be referred to an expert physician specialized or experienced in teratology for advice	N/A	N/A	
7) Of the need to contact their doctor immediately upon suspicion of pregnancy	N/A	N/A	
8) To not share the medicinal product with any other person			
9) That they should not donate blood during treatment (including during dose interruptions) and for at least 4 weeks following discontinuation of Thalidomide			
10) That they should return the unused capsules to the pharmacist at the end of treatment			
11) That Thalidomide is found in semen, so there is a need to use condoms during the treatment and 4 weeks after discontinuation		N/A	N/A

12) That if his partner becomes pregnant, he should inform his treating doctor immediately and always use a condom		N/A	N/A
13) That he should not donate semen during treatment (including during dose interruptions) and for at least 4 weeks following discontinuation of Thalidomide		N/A	N/A
Can you confirm that your patient:	**Male Patients**	**Women of Non-childbearing Potential***	**Women of Childbearing Potential**
14) Was referred to a contraceptive consultant, if required?	N/A	N/A	
15) Is capable of complying with contraceptive measures?		N/A	
16) The patient is aware of the risk of contraceptive failure		N/A	
17) Agreed to undergo pregnancy testing at least in 4 weekly intervals (including days intervals throughout treatment and also for a period of 4 weeks after stopping treatment) unless confirmed tubal sterilization? This includes women of childbearing potential who confirm absolute and continued abstinence.	N/A	N/A	
18) Had a negative pregnancy test before starting treatment even if absolute and continued abstinence?	N/A	N/A	

* Refer to section "Prescribing Thalidomide" for criteria to determine if patient is a woman of non-childbearing potential.

Description of the Pregnancy Prevention Programme and Patient Categorisation Algorithm



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