Thalidomide Celgene®
Pregnancy Prevention Programme

Information for Healthcare Professionals

Prescribing or Dispensing Thalidomide Celgene®

Celgene representative contact details:
AM Mangion Ltd, Regulatory Office, “Mangion Building”, New Street Off Valletta Road, Luqa.
Phone: +356 239 76333
Fax: +356 239 76123
Email: pv@ammangion.com.mt
Medical Information queries: pv@ammangion.com.mt

This booklet is intended for healthcare professionals involved in prescribing or dispensing Thalidomide Celgene®, and contains information about:

- **Preventing harm to unborn babies:** If Thalidomide Celgene® is taken during pregnancy it can cause severe birth defects or death to an unborn baby.

- **Other side effects of Thalidomide Celgene®:** The most commonly observed adverse reactions associated with the use of Thalidomide Celgene® in combination with melphalan and prednisone are: neutropenia, leukopenia, constipation, somnolence, paraesthesia, peripheral neuropathy, anaemia, lymphopenia, thrombocytopenia, dizziness, dysaesthesia, tremor and peripheral oedema. Further information and recommended precautions can be found in the Thalidomide Celgene® Summary of Product Characteristics (SmPC).

- **Thalidomide Celgene® Pregnancy Prevention Programme:** This Programme is designed to make sure that unborn babies are not exposed to Thalidomide Celgene®. It will provide you with information about how to follow the programme and explain your responsibilities.

This booklet will help you understand these problems and make sure you know what to do before prescribing and dispensing Thalidomide Celgene®.

For your patients' own health and safety, please read this booklet carefully. You must ensure that your patients fully understand what you have told them about Thalidomide Celgene® before starting treatment.

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Introduction

Thalidomide Celgene® belongs to a group of medicines known as 'immunomodulatory' medicines. As the prescribing physician or pharmacist, you play a central role in ensuring that Thalidomide Celgene® is used safely and correctly.

Despite thalidomide's confirmed association with birth defects in the early 1960's, the usefulness of this drug in the treatment of many disease conditions has emerged.

Large trials have demonstrated the use of Thalidomide Celgene® as an effective treatment for enhancing response rates and increasing survival in patients with multiple myeloma. Thalidomide Celgene® in combination with melphalan and prednisone is now approved across Europe for the first-line treatment of multiple myeloma, with the following indication:

> Thalidomide Celgene® in combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.
>
> Thalidomide Celgene® is prescribed and dispensed according to the Thalidomide Celgene® Pregnancy Prevention Programme

The recommended oral dose is 200 mg per day, and a maximum number of 12 cycles of 6 weeks should be used. Thalidomide Celgene® should be taken as a single dose at bedtime, to reduce the impact of somnolence. Thalidomide Celgene® can be taken with or without food.

This booklet is part of the 'Thalidomide Celgene® Pregnancy Prevention Programme', which is necessary because if Thalidomide Celgene 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 booklet will describe your responsibilities as a prescriber or a pharmacist, and will summarise the information that you need to tell your patient to ensure they are aware of the risks and their responsibilities.

All of the Thalidomide Celgene® Pregnancy Prevention Programme materials are contained within the 'Educational Healthcare Professional's Kit', and additional copies can be obtained by using the contact details displayed on the front of this booklet. These materials can be used for counselling patients on the risks of Thalidomide Celgene® and the precautions to be taken.

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

Thalidomide Celgene® warning:
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 Celgene® Pregnancy Prevention Programme are met. The conditions of the Thalidomide Celgene® Pregnancy Prevention Programme must be fulfilled for all male and female patients.

Teratogenicity: Potential or Actual Foetal Exposure to Thalidomide Celgene

Thalidomide Celgene® must never be used by women who are pregnant, as just a single dose (one capsule) can induce a high frequency of severe and life-threatening birth defects. Thalidomide Celgene® must never be used by women who are able to become pregnant unless they follow the Thalidomide Celgene® Pregnancy Prevention Programme. Since thalidomide may be present in the semen of male patients, male and female patients must both follow pregnancy prevention measures.

If a female patient misses, or is suspected to have missed her period or has any abnormality in menstrual bleeding, or suspects she is pregnant, then:

- Thalidomide Celgene® must be discontinued immediately
- The woman must have a pregnancy test
- If the pregnancy test is positive, the woman should be referred to a physician experienced in teratology for further evaluation and counselling.

If pregnancy occurs in a partner of a male patient taking Thalidomide Celgene®, the female partner should be referred to a physician specialised or experienced in teratology for evaluation and advice. The male patient must inform his doctor immediately.

Any positive pregnancy test or suspected foetal exposure to Thalidomide Celgene® must be reported immediately to the regulatory authorities (by the normal reporting route for adverse events) and also to the AM Mangion Ltd Drug Safety department. Your 'Educational Healthcare Professional's Kit' contains a pregnancy reporting form that you should use.

Thalidomide Celgene® and Other Potential Side Effects

In addition to the teratogenic effects of Thalidomide Celgene®, there are several other potential side effects your patient should be aware of. Please refer to the **Thalidomide Celgene Summary® of Product Characteristics (SmPC)** for full information about these side effects and recommended precautions, which include:

• **Venous and arterial thromboembolic events:** Patients treated with Thalidomide have an increased risk of venous and arterial thromboembolic events (mainly deep vein thrombosis, pulmonary embolism, myocardial infarction and cerebrovascular events).
Thromboprophylaxis should be administered for at least the first 5 months of treatment especially in patients with additional thrombotic risk factors. Prophylactic antithrombotic medicines, such as low molecular weight heparins or warfarin, should be recommended. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors.

Concomitant administration of erythropoietic agents or previous history of thromboembolic events may also increase the thromboembolic risk in these patients. Action should be taken to try to minimize all modifiable risk factors (e.g. smoking cessation, control of hypertension and hyperlipidaemia).
Patients with known risk factors for thromboembolism including previous thrombosis should be closely monitored.
Patients should be informed about this risk and should be advised to look out for the signs and symptoms of thromboembolism.

If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the thalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of thalidomide treatment.

• **Peripheral neuropathy:** this is a very common, potentially severe, adverse reaction of treatment with thalidomide that may result in irreversible damage. Peripheral neuropathy generally occurs following chronic use over a period of months and in a Phase 3 study the median time to first neuropathy event was 42.3 weeks. However, there are reports of neuropathy following relatively short-term use.

It is recommended that clinical and neurological examinations are performed in patients prior to starting thalidomide therapy, and that routine monitoring is carried out regularly during treatment. Medicinal products known to be associated with neuropathy should be used with caution in patients receiving thalidomide. If the patient experiences peripheral neuropathy, the following dose and schedule modifications should be introduced:

Table 1: Recommended dose modifications for Thalidomide Celgene® 50mg hard capsules related neuropathy.

Severity of neuropathy	Modification of dose and regimen
Grade 1 (paraesthesia, weakness and/or loss of reflexes) with no loss of function	Continue to monitor the patient with clinical examination. Consider reducing dose if symptoms worsen. However, dose reduction is not necessarily followed by improvement of symptoms.
Grade 2 (interfering with function but not with activities of daily living)	Reduce dose or interrupt treatment and continue to monitor the patient with clinical and neurological examination. If no improvement or continued worsening of the neuropathy, discontinue treatment. If the neuropathy resolves to Grade 1 or better, the treatment may be restarted, if the benefit/risk is favourable.
Grade 3 (interfering with activities of daily living)	Discontinue treatment
Grade 4 (neuropathy which is disabling)	Discontinue treatment

• **Syncope and bradycardia:** Patients should be monitored for syncope and bradycardia and dose reduction or discontinuation may be required.

• **Skin reactions:** If at anytime the patient experiences a toxic skin reaction e.g. Stevens-Johnson, the treatment should be discontinued permanently.

• **Somnolence:** Thalidomide frequently causes somnolence. Therefore, Thalidomide should be taken as a single dose at bedtime. Patients should be instructed to avoid situations where somnolence may be a problem and to seek medical advice before taking other medicinal products known to cause somnolence. Patients should be monitored and dose reduction may be required.

Your patient should be encouraged to report any unusual reactions or side effects from their medication to their prescriber. The side effects listed are also described in the patient information booklet and in the Thalidomide Celgene® product information leaflet, which patients should take home and read thoroughly.

Healthcare Professional Obligations

Healthcare professionals have specific obligations that must be followed when prescribing or dispensing Thalidomide Celgene®, which are:

Prescriber: You must ensure that

• Your patient is fully educated on the risks of Thalidomide Celgene®.

• You complete the appropriate 'Treatment Initiation Form' along with your patient before the first prescription is issued.

• If relevant, your patient is using the appropriate pregnancy prevention measures.

• Female patients of childbearing potential receive a pregnancy test, which must be negative, before every prescription that you issue.

• You complete a 'Patient Card' with each prescription.

• You prescribe Thalidomide Celgene® in accordance with the measures described in this booklet and the SmPC.

Pharmacist: You must ensure that

• You check and validate the 'Patient Card' prior to dispensing Thalidomide Celgene®.

• You dispense Thalidomide Celgene® in accordance with the measures described in this booklet and the SmPC.

• You remind patients of key education messages each time Thalidomide Celgene® is dispensed.

- You provide a copy of the patient information leaflet in Maltese when dispensing Thalidomide Celgene®.

Information for Prescribers

Introduction

As the prescribing physician, you play a central role in ensuring that Thalidomide Celgene® is used safely and correctly.

Most importantly, you will be helping to ensure that your patients understand the risks involved in taking Thalidomide Celgene® 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 Celgene® Pregnancy Prevention Programme. This will help to prevent any delays in your patients receiving their treatment.

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

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

Patient counselling and education

Because of the different levels of risk, you will need to communicate different things to men and women. You must ensure that your patient understands the information before they complete their section of the 'Treatment Initiation Form'.

Please ensure that you provide each patient with the relevant patient booklet, which are contained in your 'Educational Healthcare Professional's Kit'. Further copies can be obtained free of charge by using the contact details displayed on the front of this booklet.

Specific advice for female patients

Your female patients must be counselled on the risks and benefits of Thalidomide Celgene® therapy including the risk of birth defects, other side effects and important precautions associated with Thalidomide Celgene® therapy.

Animal studies have shown excretion of Thalidomide Celgene® in breast milk, but it is not known if this occurs in humans. Therefore breast-feeding should be discontinued during Thalidomide Celgene® 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 Celgene®, it is important to determine whether your patient is or is not of childbearing potential.

• **Women not of childbearing potential** include women who

- Are age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year*
- Or have
    - Premature ovarian failure confirmed by a specialist gynaecologist
    - Previous bilateral salpingo-oophorectomy, or hysterectomy
    - XY genotype, Turner's syndrome, uterine agenesis

  *Ammenorrhea following cancer therapy or during lactation does not rule out childbearing potential.

• **Women of childbearing potential** are all other women who are menstruating or perimenopausal, even those who abstain from sexual intercourse.

If your patient is a female child or adolescent then please note that Thalidomide Celgene® is not recommended for use in children below 18 years of age as safety and efficacy have not been established, and any such use would be outside the approved indication. If you decide to treat a child or adolescent with Thalidomide Celgene® then all of the conditions of the Pregnancy Prevention Programme apply. Based on the age of the patient you must carefully consider how to proceed with education and counselling regarding pregnancy prevention measures, and evaluate when to involve the patients' parent or guardian. The possibility of female patients becoming pregnant from the age of 8 years (the accepted lower age of menarche) should be considered.

Pregnancy prevention

Women of childbearing potential must understand the need to avoid pregnancy, and these patients must be adequately counselled regarding the use of pregnancy prevention measures every time a prescription is issued.

Women of childbearing potential must use one effective method of pregnancy prevention for at least 4 weeks before therapy, during therapy and even in case of dose interruptions, and at least for 4 weeks after stopping Thalidomide Celgene® therapy. This must be followed unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis.

If your patient is not established on an effective method of pregnancy prevention, they must be referred to an appropriately trained health care professional for advice in order that a pregnancy prevention method can be initiated.

The following are effective methods of pregnancy prevention:

- Subcutaneous hormonal Implant
- Levonorgestrel-releasing intrauterine system (IUS)
- Medroxyprogesterone acetate depot
- Tubal sterilisation
- Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
- Ovulation inhibitory progesterone-only pills (i.e., desogestrel)

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 method listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception.

If your patient needs to change or stop her pregnancy prevention method during her Thalidomide Celgene® therapy, she must understand the need to discuss this first with:

- The physician prescribing her pregnancy prevention method
- The physician prescribing her Thalidomide Celgene®

If a woman of childbearing potential has sexual contact without using a pregnancy prevention method while taking Thalidomide Celgene®, or believes for any reason that she may be pregnant, she must stop treatment and consult her doctor immediately.

Pregnancy testing

For women of childbearing potential you must perform a pregnancy test prior to issuing a prescription. This may be embarrassing for some patients and may need to be handled sensitively. A pregnancy test is required even if the patient has not had heterosexual intercourse since her last pregnancy test. Special consideration must be given when communicating such advice to female children.

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 Celgene® treatment can begin or continue. An inconclusive urine pregnancy test must be confirmed with a serum pregnancy test.

The pregnancy test must be performed during the consultation when Thalidomide Celgene® is being prescribed, or in the 3 days prior. Further pregnancy tests must then be performed every 4 weeks during Thalidomide Celgene® treatment, and a final test conducted at least 4 weeks after treatment ends.

A pregnancy test must be performed immediately if a patient misses her period, if there is any abnormality in menstrual bleeding, if she has heterosexual intercourse without using a pregnancy prevention method, or if she suspects she is pregnant.

If a female patient has a positive pregnancy test, then:

- **Stop treatment immediately**
- **Refer the patient to a physician specialised or experienced in dealing with teratology for advice and evaluation**
- **Complete a pregnancy reporting form as provided in the '**Educational Healthcare Professional's Kit'**, and send to the AM Mangion Ltd Drug Safety department**
- **Report the pregnancy to regulatory authorities (by the normal reporting route for adverse events).**

Specific Advice for Male Patients

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

Patients must be informed not to donate semen during or within 1 week after stopping treatment.

Pregnancy prevention

As thalidomide is present in semen male patients must be instructed to use a condom (even if vasectomised) every time they have sexual intercourse if their partner is pregnant or is of child-bearing potential and not using an effective pregnancy prevention method**.** Condoms must be used during treatment, and for 1 week after treatment has finished.

If your patient is a male adolescent then please note that Thalidomide Celgene® is not recommended for use in children below 18 years of age as safety and efficacy have not been established, and any such use would be outside the approved indication. If you decide to treat a child or adolescent with Thalidomide Celgene® then all of the conditions of the Pregnancy Prevention Programme apply. Based on the age of the patient you must carefully consider how to proceed with education and counselling regarding pregnancy prevention measures, and evaluate when to involve the patients' parent or guardian.

If the partner of a male patient becomes pregnant, then he must inform his doctor immediately.

Advice for all Patients

Your patient must be informed not to donate blood during or within one week after stopping treatment. If they discontinue therapy, they must return any unused Thalidomide Celgene® to the pharmacy.

They must also understand that their Thalidomide Celgene® 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

Prescribing Thalidomide Celgene®

Before issuing the initial prescription, you must:

- Counsel the patient on the safe use of Thalidomide Celgene® in accordance with the measures described in this booklet and the SmPC
- Obtain their written confirmation (using the correct 'Treatment Initiation Form') that they have received and understood this information
- Retain a copy of the written confirmation, and provide a copy to the patient.

A 'Patient Card' must be provided to the patient with each Thalidomide Celgene® prescription, and this will contain:

- Confirmation that they have received counselling on the safe use of Thalidomide Celgene®
- Patient category (women of childbearing potential, women of non-childbearing potential, or male)
- For women of childbearing potential, the pregnancy test date and result.

For women of childbearing potential, prescriptions of Thalidomide Celgene® should be limited to 4 weeks of treatment and continuation of treatment requires a new prescription. 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 either the prescription or the last pregnancy test date, whichever comes first.

For all other patients, prescriptions of Thalidomide Celgene® should be limited to 12 weeks and continuation of treatment requires a new prescription.

Follow-up consultations

• **Repeat or subsequent prescriptions:** the patient must return for every repeat prescription of Thalidomide Celgene®. You may prescribe a maximum of four weeks of therapy for women of childbearing potential, or twelve weeks of therapy for all other patients.

Thalidomide Celgene® treatment must be initiated and monitored under the supervision of physicians with expertise in managing immunomodulatory or chemotherapeutic agents and a full understanding of the risks of thalidomide therapy and monitoring requirements.

If a patient is transferred or consulted by another prescriber, the initial prescriber must remind them to contact Celgene and obtain a Thalidomide Celgene® 'Educational Healthcare Professional's Kit'.

• **Pregnancy testing:** for women of childbearing potential, you will need to undertake a repeat pregnancy test even if the patient has not had sexual contact since the last test. Further information regarding pregnancy testing is provided in the pregnancy testing section.

• **Counselling and pregnancy prevention advice:** you must repeat any counselling on the risks of taking Thalidomide Celgene® and repeat any pregnancy prevention advice.

Information for Pharmacists

Introduction

As a pharmacist you play an important role in ensuring that Thalidomide Celgene® is used safely and correctly.

Ordering Thalidomide Celgene®

Thalidomide Celgene can only be ordered directly from AM Mangion Ltd, (the local agent), and orders can be placed via phone, fax or email using the details shown on the front of this booklet

Dispensing Thalidomide Celgene®

You must only dispense a prescription of Thalidomide Celgene® if the prescriber has annotated the 'Patient Card', which must contain:

- Confirmation that the patient has received counselling on the safe use of Thalidomide Celgene®
- The patient category (women of childbearing potential, women of non-childbearing potential or male)
- For women of childbearing potential, the pregnancy test date and result.

If any information is missing, contact the doctor for verification prior to dispense.

For women of childbearing potential, ideally pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of Thalidomide Celgene® should occur within a maximum of 7 days of either the prescription or the last pregnancy test date, whichever comes first.

Dispensing advice

• Please ensure that you dispense Thalidomide Celgene® blisters intact; capsules must not be removed from blisters and packaged into bottles.

• For each prescription, dispense a maximum of a four-week supply for women of childbearing potential or a twelve-week supply for all other patients.

• Please educate all pharmacists within your pharmacy about the dispensing procedures for Thalidomide Celgene®.

• Instruct patients to return any unused Thalidomide Celgene® to the pharmacy. Pharmacies must accept any unused Thalidomide Celgene® returned by

patients for destruction, and follow Good Pharmacy Practice guidelines for destruction of dangerous medicines.

• Posting Thalidomide Celgene® is not recommended, but if it is necessary, it should be sent by secure courier with proof of delivery to the patient.

- Please provide a copy of the patient information leaflet in Maltese when dispensing Thalidomide Celgene®.

Patient education

At each supply of Thalidomide Celgene®, please ensure that you remind patients of the key education messages for the safe use of Thalidomide Celgene®.

Follow-up dispensing

You must not loan Thalidomide Celgene® capsules to a patient in advance of the follow-up prescription. Each follow-up prescription must only be dispensed if the prescriber has annotated the 'Patient Card' correctly, and the patient must be reminded of the key education messages.

The Thalidomide Celgene® Pregnancy Prevention Programme at a Glance

Prescriber: You must

• Communicate the risks and benefits of Thalidomide Celgene® therapy to your patient.

• Complete a 'Treatment Initiation Form' along with your patient (this only needs to be done once). Retain a copy with your records, and provide a copy to the patient.

• Provide pregnancy prevention counselling (if appropriate).

• Perform a pregnancy test (if appropriate) prior to every prescription.

• Issue 'Patient Card' to show:
    • confirmation that your patient has received counselling
    • patient category
    • pregnancy test date and result (if appropriate).

• Remind your patient of the safe use of Thalidomide Celgene® at each consultation.

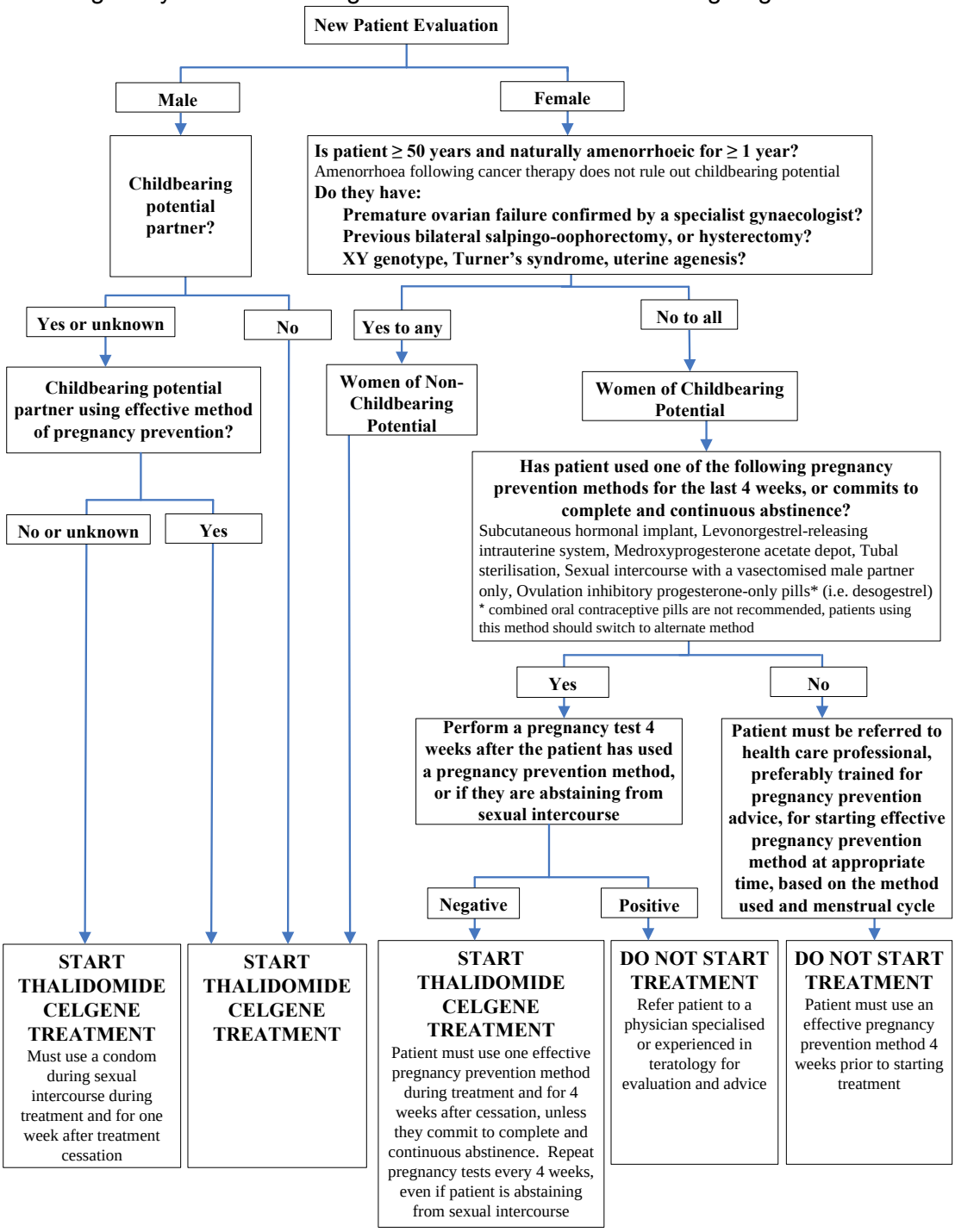
Pharmacist: You must

• Order Thalidomide Celgene® from the local agent, AM Mangiong Ltd.

• Dispense Thalidomide Celgene® only if the prescriber has annotated the 'Patient Card' correctly.

• Remind your patient of the safe use of Thalidomide Celgene®, each time a prescription is dispensed,

- The Pregnancy Prevention Programme is set out in the following Algorithm



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