Thalidomide Celgene® (thalidomide)  
*Pregnancy Prevention Programme*  

**Information for Healthcare Professionals**  
Prescribing or Dispensing Thalidomide Celgene®  

**UK**

**Celgene contact details:**  
Phone: 0808 156 3059  
Fax: 0808 156 3058  
Email: rmp.uk.ire@celgene.com
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®:**
  Some of the most commonly observed adverse reactions associated with the use of Thalidomide Celgene® in combination with melphalan and prednisone include: venous and arterial thromboembolic events, neutropenia, leukopenia, constipation, somnolence, paraesthesia, peripheral neuropathy, anaemia, lymphopenia, thrombocytopenia, dizziness, dysesthesia, tremor and peripheral oedema. A full list of all side effects, further information and recommended precautions can be found in the Thalidomide Celgene® Summary of Product Characteristics (SmPC), which can be found on the Celgene website: www.celgene.co.uk.

- **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’ 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.**
## Contents

1.0 Introduction 3
  1.1 Licensed indication and posology 3
  1.2 The Thalidomide Celgene® Pregnancy Prevention Programme 3
  1.3 Overview of the Healthcare Professional’s Information Pack 4
  1.4 Teratogenicity: Potential or Actual Foetal Exposure to Thalidomide Celgene® 5
  1.5 Safety advice relevant to all patients 6

2.0 Therapeutic management advice to avoid foetal exposure 7
  2.1 Women of non-childbearing potential 7
  2.2 Women of childbearing potential 8
  2.3 Men 10
  2.4 Advice for all Patients 11

3.0 Healthcare Professional Obligations 12
  3.1 Information for Prescribers 13
    3.1.1 Patient and healthcare professional education 13
    3.1.2 Patient counselling and education 13
    3.1.3 Prescribing Thalidomide Celgene® 14
      3.1.3.1 Maximum prescription lengths 14
      3.1.3.2 Initial prescription 14
      3.1.3.3 Repeat of subsequent prescriptions 15
    3.2 Information for Pharmacists 15
      3.2.1 Dispensing Thalidomide Celgene® 15
      3.2.2 Dispensing Advice 16

4.0 Follow-up assessment of the effectiveness of the programme 17

5.0 Safety Advice Relevant to all Patients 18
  5.1 Venous and arterial thromboembolic events 18
  5.2 Peripheral neuropathy 18
  5.3 Syncope and bradycardia 19
  5.4 Skin reactions 19
  5.5 Somnolence 20
  5.6 Tumour lysis syndrome 20
  5.7 Patients with renal or hepatic impairment 20
  5.8 Lactose intolerance 20
  5.9 Safety and off-label use 21
  5.10 Disposal of unwanted medicine 21
  5.11 Blood donation 21

6.0 Reporting Adverse Events 22
1.0 Introduction

1.1 Licensed indication and posology

Thalidomide Celgene® is licensed for use 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. 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. For full details, please refer to the Summary of Product Characteristics (SmPC), which can be found on the Celgene website: www.celgene.co.uk.

1.2 The Thalidomide Celgene® Pregnancy Prevention Programme

Thalidomide Celgene® must be prescribed and dispensed according to 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.

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.
1.3 Overview of the Healthcare Professional’s Information Pack

All of the Thalidomide Celgene® Pregnancy Prevention Programme materials are contained within the ‘Healthcare Professional’s Information Pack’, 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 ensure that your patients fully understand what you have told them about Thalidomide Celgene® before starting treatment.

Contained in this booklet is key information for Thalidomide Celgene® of relevance to healthcare professionals and contains the following:

- Thalidomide Celgene® Pregnancy Prevention Programme
  - educational information
  - therapy management advice to avoid foetal exposure to Thalidomide Celgene®
  - a distribution control system
- safety advice of relevance to all patients
- process for follow-up of effectiveness of the measures described in this pack
- process for reporting adverse events in patients treated with Thalidomide Celgene®.

In order to obtain Thalidomide Celgene®, it is a requirement of the Pregnancy Prevention Programme that all healthcare professionals ensure that they have read and understood this pack before prescribing or dispensing Thalidomide Celgene® for any patient.

- Pharmacies must register with Celgene using the Pharmacy Registration Form, to be able to order and dispense Thalidomide Celgene®.
- Prescribers must complete the appropriate Treatment Initiation Form with every patient before the first prescription is issued
- Every prescription for Thalidomide Celgene® must be accompanied by a Prescription Authorisation Form
  - this form must be signed by prescriber and pharmacist and retained for a minimum of 2 years
  - this includes instances where Thalidomide Celgene® is prescribed to in-patients or if a prescription has to be dispensed in two parts due to the unavailability of sufficient stock to fulfill the prescription.
- The Pharmacy Registration Form and Prescription Authorisation Form are in subsequent sections of this pack.
All patients should be given a Patient Booklet and Health Card to take home – these materials remind patients of the key educational information and risks of treatment, and can be found in the Information for Patients section of this pack.

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 the prescription, and the date of the last negative pregnancy test, must be within the 3 days prior to the date of the prescription.

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

This Healthcare Professional’s Information Pack also contains adverse event reporting forms, treatment checklists and algorithms, example information and forms for obtaining informed consent and an example letter to notify a general practitioner that their patient is receiving Thalidomide Celgene®.

1.4 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 described in this pack (Section 2.0). Since thalidomide may be present in the semen of male patients, all male and female patients must both follow pregnancy prevention measures.

If a female patient or female partner of a male 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.

Any positive pregnancy test or suspected foetal exposure to Thalidomide Celgene® must be reported immediately to the Medicines and Healthcare Products Regulatory Agency (MHRA) and to the Celgene Drug Safety department. In this instance you must:

- Stop treatment immediately
- Refer the patient to a physician specialised or experienced in dealing with teratology for advice and evaluation.
1.5 Safety advice relevant to all patients

In addition to information about the Pregnancy Prevention Programme, this booklet contains important advice for healthcare professionals about how to minimise the risk of adverse events during treatment with Thalidomide Celgene®.

For further information about the appropriate use and safety profile of Thalidomide Celgene® please refer to the SmPC, which can be found on the Celgene website: www.celgene.co.uk.
2.0 Therapeutic management advice to avoid foetal exposure

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.

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.

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 patient’s 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.

2.1 Women of non-childbearing potential

Women in the following groups are considered not to have childbearing potential and do not need to undergo pregnancy testing or receive contraceptive advice.

- Age ≥50 years and naturally amenorrheic for ≥1 year. Please note amenorrhoea following cancer therapy 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.

Women of childbearing potential are all other women who are menstruating or perimenopausal, even those who abstain from sexual intercourse. Treating physicians are advised to refer their patient for a gynaecological opinion if at all unsure as to whether a woman meets the criteria for being of non-childbearing potential.

If a patient does not meet at least one of above criteria, but the treating physician considers the patient to be of non-childbearing potential, then prior approval of any deviation from these stipulated criteria should be sought from the
Celgene Medical Director. This is a mandatory requirement. If there is a need for a deviation, then you should contact Celgene Risk Management (Tel: 0808 156 3059 Email: rpm.uk.ire@celgene.com). The following information is required to assess whether a patient, who does not meet at least one of the above criteria, can be treated as a women of non-childbearing potential:

- DOB and Initials of the Patient
- Details of why the physician considers the patient to be of non-childbearing potential
- Background to why a deviation has been requested.

2.2 Women of childbearing potential

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 at least 4 weeks before therapy, during therapy and even in the case of dose interruptions, and for at least a further 4 weeks after stopping Thalidomide Celgene® therapy. This must be followed unless the patient commits to absolute and continuous abstinence confirmed to her physician on a monthly basis.

If your patient is not established on an effective method of pregnancy prevention, they must be referred preferably 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 methods 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

Women of childbearing potential 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
- Notify Celgene immediately by contacting the Celgene Drug Safety Department (Tel: 0808 238 9908). Please also complete the Pregnancy Reporting Form included in this pack. Celgene will wish to follow-up with you the progress of all pregnancies.
• Report the event to the Medicines and Healthcare products Regulatory Agency (MHRA) using the ‘Yellow Card’ Scheme. Reporting forms and information can be found at www.yellowcard.gov.uk.

2.3 Men

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 found in semen, male patients must use condoms during treatment and for 1 week after dose interruption and/or cessation of treatment if their partner is pregnant or is of childbearing potential and not using an effective pregnancy prevention method.

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 patient’s parent or guardian.

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

• Refer the female partner to a physician specialised or experienced in dealing with teratology for advice and evaluation

• Notify Celgene immediately by contacting the Celgene Drug Safety Department (Tel: 0808 238 9908). Please also complete the Pregnancy Reporting Form included in this pack. Celgene will wish to follow-up with you the progress of all pregnancies.

• Report the event to the Medicines and Healthcare products Regulatory Agency (MHRA) using the ‘Yellow Card’ Scheme. Reporting forms and information can be found at www.yellowcard.gov.uk.
2.4 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 and sight of children.
3.0 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’ with your patient before the first prescription is issued
- You provide the patient with a ‘Health Card and Patient Booklet’
- 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 ‘Prescription Authorisation Form’ with every prescription
  - this includes instances where Thalidomide Celgene® is prescribed to in-patients or if a prescription has to be dispensed in two parts due to the unavailability of sufficient stock to fulfill the prescription.
- You prescribe Thalidomide Celgene® in accordance with the measures described in this booklet and the SmPC, which can be found on the Celgene website: www.celgene.co.uk.

**Pharmacist: You must ensure that**

- Your Pharmacy is registered with the Thalidomide Celgene® Pregnancy Prevention Programme. Registration will be valid for 2 years.
- Thalidomide Celgene® is only dispensed if the prescription is accompanied by a Prescription Authorisation Form
  - this includes instances where Thalidomide Celgene® is prescribed to in-patients or if a prescription has to be dispensed in two parts due to the unavailability of sufficient stock to fulfill the prescription.
- You check and validate the ‘Prescription Authorisation Form’ prior to dispensing Thalidomide Celgene®
- You dispense Thalidomide Celgene® in accordance with the measures described in this booklet
- You remind patients of key education messages each time Thalidomide Celgene® is dispensed.
3.1 Information for Prescribers

3.1.1 Patient and healthcare professional education

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 can be found on the last page of this booklet.

3.1.2 Patient counselling and education

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

Please make use of the Patient Booklet and Health Card to help explain the relevant information. Copies of the booklet are contained in your ‘Healthcare Professional’s Information Pack’, and your patient may wish to take these materials home to read in their own time or with a relative. Further copies can be obtained by using the contact details displayed on the front of this booklet.
3.1.3 Prescribing Thalidomide Celgene®

3.1.3.1 Maximum prescription lengths

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.

Approval from the Celgene Medical Director is a mandatory requirement prior to any deviation from these stipulated prescription lengths. If there is a need for an exception to the maximum prescription lengths, then you should contact Celgene Risk Management (Tel: 0808 156 3059 Email: rmp.uk.ire@celgene.com). The following information is required to assess whether a deviation to the maximum prescription length can be approved:

- DOB and Initials of the Patient
- Sex and childbearing potential
- Background to why a deviation has been requested.

3.1.3.2 Initial prescription

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, which can be found on the Celgene website: www.celgene.co.uk.
- Obtain their written confirmation (using the correct Treatment Initiation Form) that they have received and understood this information, and provide the patient with a copy
- Provide the patient with a Patient Booklet and Health Card
- A ‘Prescription Authorisation Form’ must be provided to the patient with each Thalidomide Celgene® prescription, and this will contain:
  - Patient name, date of birth and diagnosis
  - Prescriber name, signature and date
  - Patient category (women of childbearing potential, women of non-childbearing potential, or male)
– Confirmation that they have received counselling on the safe use of Thalidomide Celgene®
– For women of childbearing potential, the pregnancy test date and result.

The patient must present their ‘Prescription Authorisation Form’ to the pharmacy along with their prescription, and the pharmacy will check this form prior to dispensing Thalidomide Celgene®.

3.1.3.3 Repeat of subsequent prescriptions

The patient must return to the initial prescriber for every repeat prescription of Thalidomide Celgene®. If a patient is transferred or consulted by another prescriber, the initial prescriber must remind them to contact Celgene and obtain a Thalidomide Celgene® ‘Healthcare Professional’s Information Pack’.

3.2 Information for Pharmacists

As a pharmacist you play an important role in ensuring that Thalidomide Celgene® is used safely and correctly. Thalidomide Celgene® will only be supplied to pharmacies, who have completed a ‘Thalidomide Celgene® Pregnancy Prevention Programme, Pharmacy Registration Form’ and returned this form to Celgene.

3.2.1 Dispensing Thalidomide Celgene®

Along with each Thalidomide Celgene® prescription, prescribers must complete a Prescription Authorisation Form and instruct the patient to provide this to their pharmacy. You must only dispense Thalidomide Celgene® if the prescriber has annotated this form correctly, and it 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 negative pregnancy test date.

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 the prescription date, and the date of the last negative pregnancy test, must be within the 3 days prior to the date of the prescription.
Please retain the ‘Prescription Authorisation Form’ for 2 years.

- Every prescription for Thalidomide Celgene® must be accompanied by a Prescription Authorisation Form
  - this form must be signed by prescriber and pharmacist and retained for a minimum of 2 years
  - this includes instances where Thalidomide Celgene® is prescribed to in-patients or if a prescription has to be dispensed in two parts due to the unavailability of sufficient stock to fulfill the prescription.

3.2.2 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.
4.0 Follow-up assessment of the effectiveness of the programme

The terms of the Thalidomide Celgene® Marketing Authorisation require Celgene to assess the effectiveness of the Pregnancy Prevention Programme in order to ensure that all reasonable steps are being taken to reduce the risk of pregnancy in patients treated with Thalidomide Celgene®.

Celgene have agreed with the MHRA that pharmacies can fulfill their obligations in this respect, by conducting a manual self-audit and reporting the results to Celgene. This information will be provided, in an anonymised and aggregated format, to the MHRA and the European Medicines Agency (EMA). Celgene will supply pharmacies with an audit pack, such that annual self-auditing of pharmacies and feedback of the audit results to Celgene can occur.

It is therefore critical for pharmacies to ensure that all documentation associated with the Pregnancy Prevention Programme is completed accurately and that audit results are provided faithfully and diligently, in the interests of patient safety.
5.0 Safety Advice Relevant to all Patients

The following section contains advice to healthcare professionals about how to minimise the risk of the principal adverse events associated with the use of Thalidomide Celgene®. For a full list of the adverse events that may be associated with its use please refer to the Summary of Product Characteristics (SmPC), which can be found on the Celgene website: www.celgene.co.uk.

5.1 Venous and arterial thromboembolic events

Patients treated with thalidomide have an increased risk of venous thromboembolism (such as deep vein thrombosis and pulmonary embolism) and arterial thromboembolism (such as myocardial infarction and cerebrovascular event). The risk appears to be greatest during the first 5 months of therapy. 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, are recommended. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient’s underlying risk factors.

Previous history of thromboembolic events or concomitant administration of erythropoietic agents or other agents such as hormone replacement therapy, may also increase thrombotic risk in these patients. Therefore, these agents should be used with caution in multiple myeloma patients receiving thalidomide with prednisone and melphalan. Particularly, a haemoglobin concentration above 12g/dl should lead to discontinuation of erythropoietic agents.

Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling.

5.2 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:
5.3 Syncope and bradycardia

Patients should be monitored for syncope and bradycardia and dose reduction or discontinuation may be required.

5.4 Skin reactions

If at anytime the patient experiences a toxic skin reaction e.g. Stevens-Johnson Syndrome, the treatment should be discontinued permanently.

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

<table>
<thead>
<tr>
<th>Severity of neuropathy</th>
<th>Modification of dose and regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong> (paraesthesia, weakness and/or loss of reflexes) with no loss of function</td>
<td>Continue to monitor the patient with clinical examination. Consider reducing dose if symptoms worsen. However, dose reduction is not necessarily followed by the improvement of symptoms</td>
</tr>
<tr>
<td><strong>Grade 2</strong> (interfering with function but not with activities of daily living)</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Grade 3</strong> (interfering with activities of daily living)</td>
<td>Discontinue treatment</td>
</tr>
<tr>
<td><strong>Grade 4</strong> (neuropathy which is disabling)</td>
<td>Discontinue treatment</td>
</tr>
</tbody>
</table>
5.5 Somnolence

Thalidomide frequently causes somnolence. Therefore, Thalidomide Celgene® 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.

Patients should be advised as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks.

5.6 Tumour lysis syndrome

The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

5.7 Patients with renal or hepatic impairment

Patients with severe renal or hepatic impairment should be carefully monitored for adverse effects.

5.8 Lactose intolerance

The capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
5.9 Safety and off-label use

Please note that the posology, adverse event profile and recommendations outlined above, relate to the use of Thalidomide Celgene® within its licensed indication.

Thalidomide Celgene® must always be used according to the Pregnancy Prevention Programme described in this pack – these precautions must be followed, irrespective of the treatment setting, including the indication for treatment.

It is essential that the patient’s diagnosis is entered on the Prescription Authorisation Form - this will allow an assessment of the clinical usage of Thalidomide Celgene®, which is important for ongoing monitoring of safety.

5.10 Disposal of unwanted medicine

Patients must be advised never to give Thalidomide Celgene® to another person and to return any unused capsules to their pharmacist at the end of the treatment.

5.11 Blood donation

Patients should not donate blood during treatment and for 1 week after cessation of treatment with Thalidomide Celgene®.
6.0 Reporting Adverse Events

The safe use of Thalidomide Celgene® is of paramount importance.

Adverse events (and cases of suspected or confirmed pregnancy or foetal exposure) should be reported. Adverse event report forms and pregnancy reporting forms are included in this pack and should be forwarded to the Celgene Drug Safety Department (Tel: 0808 238 9908 Fax: 0844 801 0468; Email: drugsafetyuk@celgene.com).

The event should also be reported to the MHRA via the 'Yellow Card' scheme. Reporting forms and information can be found at www.yellowcard.gov.uk.
Contact Details

Risk Management:
For information and questions on the risk management of Celgene’s products, the Pregnancy Prevention Programme and pharmacy registrations.
Tel: 0808 156 3059
Fax: 0808 156 3058
Email: rmp.uk.ire@celgene.com

Drug Safety:
To report any adverse events to Celgene.
Tel: 0808 238 9908
Fax: 0844 801 0468
Email: drugsafetyuk@celgene.com
Adverse events can also be reported to the MHRA using a ‘Yellow Card’ – reporting forms and information can be found at www.yellowcard.gov.uk.

Medical Information:
To obtain Medical Information on Celgene’s products.
Tel: 0844 801 0045
Fax: 0844 801 0046
Email: medinfo.uk.ire@celgene.com

Website:
Reference safety information (including the summary of product characteristics) and educational materials for all of Celgene’s products are available from our website - www.celgene.co.uk

Distributor:
For product delivery enquiries.

In Great Britain
Movianto UK Ltd
1 Progress Park
Elstow
Bedford
MK42 9XE
Tel: 01234 248632
Fax: 01234 248705
Email: orders.uk@movianto.com

In Northern Ireland
Sangers Ltd
2 Marshalls Road
Belfast
BT5 6SR
Tel: 02890 402719
Fax: 02890 705623

© Celgene Limited 2011