Celgene Limited
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Berkshire
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[01/08/08]

IMPORTANT SAFETY INFORMATION

Dear Healthcare Professional,

Following discussions with the European Medicines Agency (EMEA) and the Irish Medicines Board (IMB), this letter has been sent, to draw your attention to the potential risks of treatment with Thalidomide Pharmion™ – including the risk of teratogenicity – and to explain how you must follow the Thalidomide Pharmion **Pregnancy Prevention Programme** (PPP) in order to obtain and dispense Thalidomide Pharmion appropriately.

Upon commercial launch of Thalidomide Pharmion (currently scheduled for Monday 8th September), the Pharmion Risk Management Programme (PRMP) will cease to operate, and be replaced by the Thalidomide Pharmion PPP.

Supply of Thalidomide Pharmion under the PPP is subject to the dispensing pharmacy and prescribing physician first registering with the Thalidomide Pharmion PPP, by completing the registration forms supplied in the Thalidomide Pharmion Healthcare Professionals Educational Kit (see details below) and returning these forms to Celgene.

Those pharmacies and physicians currently supplying patients with unlicensed Thalidomide Pharmion should register with the Thalidomide Pharmion PPP to avoid interruption in the supply of thalidomide for their patients.

Thalidomide Pharmion 50 mg hard capsules have been granted a European Marketing Authorisation for use in combination with melphalan and prednisone, as first-line treatment of patients with untreated multiple myeloma, aged $\geq$ 65 years or ineligible for high dose chemotherapy. Thalidomide 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.

Due to the powerful human teratogenic effects of Thalidomide and its important clinical risks, a Risk Management Plan has been implemented for Thalidomide in agreement with the EMEA and The Irish Medicines Board (IMB). This plan includes a **Pregnancy Prevention Programme (PPP)** to avoid any thalidomide exposure during pregnancy. The Thalidomide Pharmion Pregnancy Prevention Programme is necessary because if Thalidomide Pharmion is taken during pregnancy it can cause severe birth defects or death to an unborn baby. In the 1950s and 1960s,

thalidomide was prescribed to pregnant women as a sedative and to relieve morning sickness. As a result approximately 12,000 children were born with severe birth defects caused by thalidomide, approximately 5,000 survive today.

The Pregnancy Prevention Programme also includes the monitoring of other clinically important risks associated with thalidomide, such as peripheral neuropathy and thromboembolism and the provision of educational materials. These educational materials are contained within the Thalidomide Pharmion Healthcare Professionals Educational Kit and include the following:

- Thalidomide Pharmion 50 mg hard capsules Summary of Product Characteristics (SPC)
- Healthcare professionals booklet including all information needed on the measures which should be followed for initiating and continuing treatment
- Pharmacy registration form.
- Physician registration form.
- Prescription authorisation form
- Treatment initiation forms for patients
- Patient information booklets
- Patient card
- Patient assessment algorithm
- Specific report forms in case of pregnancy, neuropathy and adverse event.

The 'Thalidomide Pharmion Healthcare Professional's Educational Kit' will be sent to healthcare professionals involved in dispensing or prescribing Thalidomide Pharmion.

We wish to inform you about ***the following*** important safety information for the clinical use of Thalidomide Pharmion. Practical details on the restrictions for prescribing and dispensing Thalidomide in this country are included beneath the important safety information.

Undesirable effects

Most patients taking thalidomide can be expected to experience adverse reactions. The most commonly observed adverse reactions associated with the use of thalidomide in combination with melphalan and prednisone are: neutropenia, leukopenia, constipation, somnolence, paraesthesia, peripheral neuropathy, anaemia, lymphopenia, thrombocytopenia, dizziness, dysaesthesia, tremor and peripheral oedema.

The clinically important adverse reactions (see Sections 1–6 below) associated with the use of thalidomide in combination with melphalan and prednisone or dexamethasone include: teratogenicity, peripheral neuropathy, deep vein thrombosis and pulmonary embolism, syncope, bradycardia, severe skin reactions including Stevens Johnson Syndrome and toxic epidermal necrolysis, somnolence and dizziness (also see sections 4.2, 4.4 and 4.5 of the summary of product characteristics).

1) Teratogenicity and Pregnancy Prevention Programme

Thalidomide is a powerful human teratogen, a single dose of Thalidomide Pharmion 50 mg hard capsules taken by a pregnant woman can cause **severe birth defects** or foetal death. In the 1950s and 1960s thalidomide was prescribed to pregnant women as a sedative and to relieve nausea and vomiting in pregnancy. As a result 10,000 to 12,000 children were born with severe birth defects caused by thalidomide, and many are still alive today.
Thalidomide Pharmion 50 mg hard capsules is therefore contraindicated during pregnancy and all the conditions of the Thalidomide Pharmion Pregnancy Prevention Programme must be fulfilled for all male and female patients.

Multiple myeloma is a disease predominantly found in an elderly population. However, younger women of childbearing potential can be part of the patient population. All women who do not meet the criteria as defined in section 4.4 of the SPC should be considered of childbearing potential.

Prior to starting treatment with Thalidomide Pharmion

Requirements for all patients

- All patients should be fully educated regarding the teratogenic effects of thalidomide, advised that thalidomide must not be given to any other person, that they should return unused capsules to the pharmacist, and that they should not donate blood during or up to 1 week after treatment.
- All patients should be assessed and categorized into one of the following three categories: women of childbearing potential, women of non-childbearing potential and male patients. These categories define the education and risk minimization measures that should be followed. All female patients or female partners of a male patient should beconsidered of childbearing potential unless they meet the criteria defined in section 4.4 of the SPC.
- All patients should complete a 'Treatment Initiation Form' corresponding to their risk category. The prescriber should retain the completed form and provide a copy to the patient. This form documents that the patient has received all the necessary information and has understood the key education messages.
- All patients should receive a patient information booklet that summarizes the measure of the PPP to be followed and safety messages.

Specific requirements for Women of Childbearing Potential

- Contraception: All women of childbearing potential must be using an effective method of contraception for 4 weeks before therapy is commenced, unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis. If not established on effective contraception, the patient must be referred to an appropriately trained health care professional for contraceptive advice in order that contraception can be initiated. Examples of effective methods of contraception have been detailed in the section 4.4 of the SPC. Because of the increased risk of venous thromboembolism in patients with multiple myeloma, **combined oral contraceptive pills are not recommended** (See sections 4.4 and 4.5 of the SPC).
- Pregnancy testing: Once the patient had been using effective contraception for at least 4 weeks, a medically supervised pregnancy test should be performed within the 3 days prior to the visit to the prescriber. The test should ensure the patient is not pregnant when she starts treatment with thalidomide.

- Prescription Restrictions: Thalidomide Pharmion should be limited to 4 weeks of treatment; continuation of treatment requires a new prescription
- Dispensing Restrictions: Pharmacists may not dispense more than 4 weeks supply for women of childbearing potential

Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of Thalidomide Pharmion 50 mg hard capsules should occur within a maximum of 7 days of the prescription.

Specific requirements for Women of Non-Childbearing Potential and Male patients

- Prescription Restrictions: Thalidomide Pharmion should be limited to 4 weeks of treatment; continuation of treatment requires a new prescription
- Dispensing Restrictions: Pharmacists may not dispense more than 4 weeks supply for women of non-childbearing potential and male patients

Dispensing of Thalidomide Pharmion 50 mg hard capsules should occur within a maximum of 7 days of the prescription.

Thalidomide Pharmion PPP registration, prescribing and dispensing procedures

Overview

- The pharmacy wishing to dispense Thalidomide Pharmion and the physician wishing to prescribe must complete their respective registration forms and fax these forms to Celgene Limited.
- Thalidomide Pharmion will not be supplied unless the receiving pharmacy is registered and the order quotes the name of a registered physician.
- Each patient must be counselled to ensure they understand the risks of treatment, and pregnancy prevention measures instigated as appropriate.
- The prescribing physician must complete a treatment initiation form to initiate therapy with Thalidomide Pharmion, and also a prescription authorisation form to accompany each prescription.
- The dispensing pharmacist must cross-check and countersign the prescription authorisation form with each dispense.
- Patient materials must be supplied to each patient (booklet and card).

Thalidomide Pharmion Pregnancy Prevention Programme – Pharmacy Registration Form

- Any pharmacy wishing to dispense Thaliomide Pharmion must complete a pharmacy registration form, and fax the completed form to Celgene Limited.
- The pharmacy registration form obligates the pharmacy to instigate certain pregnancy prevention measures, in particular to:
    - require understanding of the 'Healthcare Professionals Educational Kit'
    - instigate the prescription authorisation form
    - limit dispensing to within 7 days of the prescription date and within 10 days of a negative, medically-supervised pregnancy test
    - limit the dispensing volume of Thalidomide Pharmion to a 4-week supply
    - assist Celgene with assessment of the effectiveness of these measures.

Thalidomide Pharmion Pregnancy Prevention Programme – Physician Registration Form

- Any physician wishing to prescribe Thaliomide Pharmion must complete a registration form, and fax the completed form to Celgene Limited.

- This registration form obligates the physician to instigate certain pregnancy prevention measures, in particular to:
    - require understanding of, and compliance with the 'Healthcare Professionals Educational Kit'
    - complete a 'Treatment Initiation Form' prior to first dispense
    - instigate the prescription authorisation form
    - limit prescribing to within 3 days of a negative, medically-supervised pregnancy test
    - limit the dispensing volume of Thalidomide Pharmion to a 4-week supply

Thalidomide Pharmion Pregnancy Prevention Programme – Treatment initiation form

- Prior to initiation of treatment with Thalidomide Pharmion, a 'Treatment Initiation Form' must be completed for each new patient.
- The 'Treatment Initiation Form' documents that the patient has been fully counselled as to the risks of treatment, and that pregnancy prevention measures have been instigated as appropriate.
- The patient should receive a copy of the completed form to keep as a reference.

Thalidomide Pharmion Pregnancy Prevention Programme Prescription authorisation form

- A 'Prescription Authorisation Form' must accompany each prescription for Thalidomide Pharmion, and each form must be checked for completeness by the dispensing pharmacist.
- The 'Prescription Authorisation Form' documents that:
    - the patient has been appropriately counselled
    - relevant pregnancy prevention measures are in place
    - dispensing is taking place within 7 days of the prescription date and within 10 days of a negative, medically-supervised pregnancy test
    - the prescribing physician and dispensing pharmacist have read and understood the Thalidomide Pharmion Healthcare Professional's Educational Kit
    - the dispensing volume of Thalidomide Pharmion is limited to a 4-week supply.

During and After Treatment with Thalidomide Pharmion

Specific requirements for Women of Childbearing Potential

- Contraception: Continue to use the effective method of contraception during therapy and for 4 weeks after stopping thalidomide therapy and even in case of temporary dose interruption
- Pregnancy testing: Perform a medically supervised pregnancy test every 4 weeks, including 4 weeks after the end of treatment. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

Specific requirement for Male Patients

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 effective contraception.

2) Peripheral neuropathy

Thalidomide is known to cause nerve damage that may be permanent (see section 4.4 and 4.8 of the SPC). Peripheral neuropathy is a very common, potentially severe, adverse reaction which

generally occurs following chronic use over a period of months. However, there are reports of neuropathy following relatively short-term use.

It is recommended to perform clinical and neurological examinations in patients prior to starting thalidomide therapy, and to carry out routine monitoring regularly during treatment (see section 4.4 of the SPC). Medicinal products known to be associated with neuropathy should be used with caution in patients receiving thalidomide (see section 4.5 of the SPC).

If the patient experiences peripheral neuropathy, dosage delay, reduction or discontinuation may be necessary. Please refer to the recommended dose modifications (section 4.2 of the SPC) below.

Table 1: Recommended dose modifications for Thalidomide Pharmion related neuropathy in first line treatment of multiple myeloma.

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 by up to 50% if symptoms worsen.
Grade 2 (interfering with function but not with activities of daily living)	Reduce dose by up to 50% 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 at 50% of the last dose, if the benefit/risk is favourable.
Grade 3 (interfering with activities of daily living)	Discontinue treatment
Grade 4 (neuropathy which is disabling)	Discontinue treatment

3) Thromboembolic events

An increased risk of deep venous thrombosis and pulmonary embolism, especially during the first five months of treatment, has been reported in patients treated with thalidomide (see sections 4.4 and 4.8 of the SPC). Patients should be informed about this risk and should be advised to look out for the signs and symptoms of thromboembolism. Thromboprophylaxis should be administered for at least the first 5 months of treatment especially in patients with additional thrombotic risk factors (e.g. concomitant administration of erythropoietic agents or previous history of DVT) (See Section 4.2 of the SPC).

4) Syncope and bradycardia

As bradycardia has been reported with thalidomide, patients should be monitored for syncope and bradycardia. Dose reduction or discontinuation may be required (see sections 4.4 and 4.8 of the SPC).

Caution should be exercised with medicinal products having the same pharmacodynamic effect such as drugs known to induce torsades de pointe, beta blockers or anticholinesterase agents (see section 4.5 of the SPC).

5) Skin reactions
Serious dermatologic reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. If at anytime the patient experiences a toxic skin reaction e.g. Stevens-Johnson syndrome, the treatment should be discontinued permanently (see section 4.4 of the SPC).

6) Somnolence and Dizziness
Thalidomide frequently causes somnolence and dizziness. Therefore, Thalidomide Pharmion should be taken as a single dose at bedtime (see section 4.2 of the SPC).

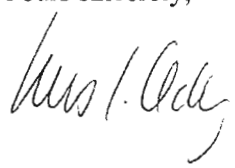
Adverse events/reactions
Suspected adverse events/reactions in patients treated with Thalidomide Phamion should be reported to Celgene by phone (1800 333 111) or fax (1800 333 112) and or to the IMB.

The content of this communication has been approved by the Committee for Medicinal products for Human Use (CHMP) and the IMB. Further information can obtained from the enclosed copy of the Thalidomide Pharmion summary of product characteristics, and also from Celgene at the address given below.

For further information please contact:

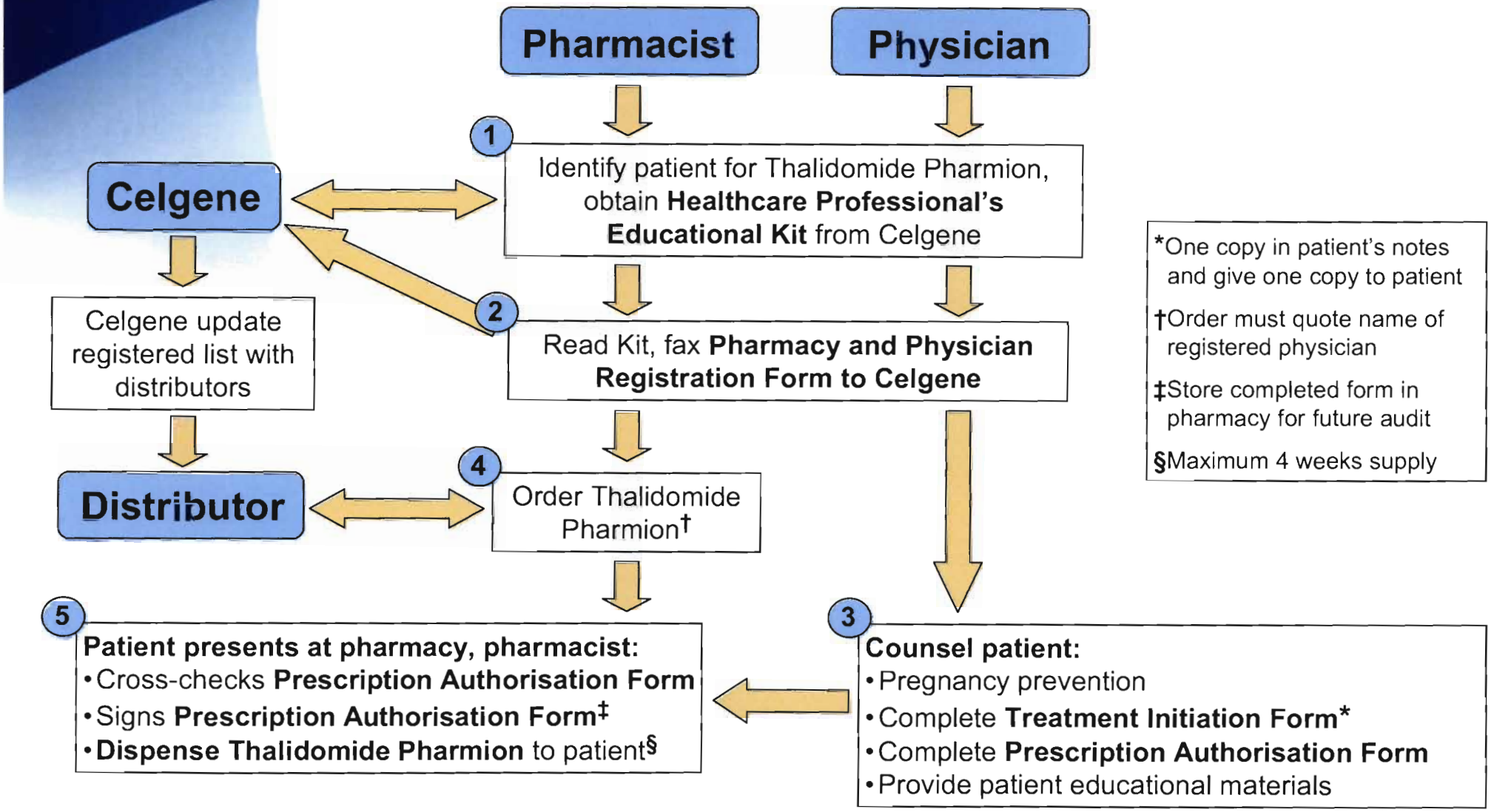
Celgene UK and Ireland Limited
Tel: 1800 992 427
Fax: 1800 992 429

Yours sincerely,



Tom Oakley
Regulatory and Drug Safety Manager
Celgene

Ireland hospital pharmacy registration and dispensing flow for Thalidomide Pharmion



Ireland community pharmacy registration and dispensing flow for Thalidomide Pharmion

*One copy in patient's notes and give one copy to patient
†Order must quote name of registered physician
‡Store completed form in pharmacy for future audit
§Maximum 4 weeks supply