

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Thalidomide Celgene 50 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg of thalidomide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

White opaque capsules marked “Thalidomide Celgene 50 mg”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 (see section 4.4).

4.2 Posology and method of administration

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 (see section 4.4).

Posology

Recommended dose

The recommended dose of thalidomide is 200 mg orally per day.

A maximum number of 12 cycles of 6 weeks (42 days) should be used.

Table 1: Starting doses for thalidomide in combination with melphalan and prednisone

Age (years)	ANC (μL)		Platelet Count (μL)	Thalidomide ^{a,b}	Melphalan ^{c,d,e}	Prednisone ^f
≤ 75	$\geq 1,500$	AND	$\geq 100,000$	200 mg daily	0.25 mg/kg daily	2 mg/kg daily
≤ 75	$< 1,500$ but $\geq 1,000$	OR	$< 100,000$ but $\geq 50,000$	200 mg daily	0.125 mg/kg daily	2 mg/kg daily
> 75	$\geq 1,500$	AND	$\geq 100,000$	100 mg daily	0.20 mg/kg daily	2 mg/kg daily
> 75	$< 1,500$ but $\geq 1,000$	OR	$< 100,000$ but $\geq 50,000$	100 mg daily	0.10 mg/kg daily	2 mg/kg daily

^a Thalidomide dosed once daily at bedtime on Days 1 to 42 of each 42-day cycle.

^b Due to the sedative effect associated with thalidomide, administration at bedtime is known to generally improve tolerability.

^c Melphalan dosed once daily on Days 1 to 4 of each 42-day cycle.

^d Melphalan dosing: reduce by 50 % for moderate (creatinine clearance: ≥ 30 but < 50 mL/min) or severe (CrCl: < 30 mL/min) renal insufficiency

^e Maximum daily melphalan dose: 24 mg (subjects ≤ 75 years old) or 20 mg (subjects > 75 years old).

^f Prednisone dosed once daily on Days 1 to 4 of each 42-day cycle.

Patients should be monitored for: thromboembolic events, peripheral neuropathy, rash/skin reactions, bradycardia, syncope, somnolence, neutropenia and thrombocytopenia (see sections 4.4 and 4.8). Dose delay, reduction or discontinuation, dependent upon the NCI CTC (National Cancer Institute Common Toxicity Criteria) grade, may be necessary.

Thromboembolic events

Thromboprophylaxis should be administered for at least the first 5 months of treatment especially in patients with additional thrombotic risk factors. Prophylactic antithrombotic medicinal products, 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 (see sections 4.4, 4.5 and 4.8).

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.

Neutropenia

White blood cell count and differential should be monitored on an ongoing basis, in accordance with oncology guidelines especially in patients who may be more prone to neutropenia. Dose delay, reduction or discontinuation, dependent upon the NCI CTC grade, may be necessary.

Thrombocytopenia

Platelet counts should be monitored on an ongoing basis, in accordance with oncology guidelines. Dose delay, reduction or discontinuation, dependent upon the NCI CTC grade, may be necessary.

Peripheral neuropathy

Dose modifications due to peripheral neuropathy are described in Table 2.

Table 2: Recommended dose modifications for Thalidomide Celgene-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 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

Elderly population

No specific dose adjustments are recommended for the elderly ≤ 75 years of age. For patients > 75 years of age, the thalidomide recommended starting dose is 100 mg per day. The initial dose of melphalan is reduced for elderly > 75 years of age considering baseline bone marrow reserve and renal function. The melphalan recommended starting dose is 0.1 to 0.2 mg/kg daily according to bone marrow reserve along with a further 50 % dose reduction for moderate (creatinine clearance: ≥ 30 but

< 50 mL/minute) or severe (CrCl: < 30 mL/minute) renal insufficiency. The maximum daily melphalan dose is 20 mg in patients > 75 years of age (see Table 1).

Patients with renal or hepatic impairment

Thalidomide Celgene has not formally been studied in patients with impaired renal or hepatic function. No specific dose recommendations for these patient populations are available. Patients with severe organ impairment should be carefully monitored for adverse reactions.

Paediatric population

There is no relevant use of Thalidomide Celgene in the paediatric population in the indication of multiple myeloma.

Method of administration

Thalidomide Celgene should be taken as a single dose at bedtime, to reduce the impact of somnolence. This medicinal product can be taken with or without food.

It is recommended to press only on one end of the capsule to remove it from the blister thereby reducing the risk of capsule deformation or breakage.

4.3 Contraindications

- Hypersensitivity to thalidomide or to any of the excipients listed in section 6.1.
- Pregnant women (see section 4.6).
- Women of childbearing potential unless all the conditions of the Thalidomide Celgene Pregnancy Prevention Programme are met (see sections 4.4 and 4.6).
- Patients unable to follow or comply with the required contraceptive measures (see section 4.4).

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

Criteria for women of non-childbearing potential

A female patient or a female partner of a male patient is considered to have childbearing potential unless she meets at least one of the following criteria:

- Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year*.
 - Premature ovarian failure confirmed by a specialist gynaecologist.
 - Previous bilateral salpingo-oophorectomy, or hysterectomy.
 - XY genotype, Turner's syndrome, uterine agenesis.
- *Amenorrhoea following cancer therapy does not rule out childbearing potential.

Counselling

For women of childbearing potential, thalidomide is contraindicated unless all of the following conditions are met:

- She understands the teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment, and 4 weeks after the end of treatment
- Even if a woman of childbearing potential has amenorrhea she must follow all the advice on effective contraception
- She should be capable of complying with effective contraceptive measures

- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy
- She understands the need to commence the treatment as soon as thalidomide is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing every 4 weeks
- She acknowledges that she understands the hazards and necessary precautions associated with the use of thalidomide.

As thalidomide is found in semen, male patients taking thalidomide must meet the following conditions:

- Understand the teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential.
- Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception.

The prescriber must ensure that:

- The patient complies with the conditions of the Thalidomide Celgene Pregnancy Prevention Programme
- The patient confirms that he (she) understand the aforementioned conditions.

Contraception

Women of childbearing potential must use one effective method of contraception for 4 weeks before therapy, during therapy, and during 4 weeks after thalidomide therapy and even in case of dose interruption 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 preferably to an appropriately trained healthcare professional for contraceptive advice in order that contraception can be initiated.

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

- 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 (see section 4.5). If a patient is currently using combined oral contraception, she 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.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/ml must be performed for women of childbearing potential as outlined below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence.

Prior to starting treatment

A medically supervised pregnancy test should be performed during the consultation, when thalidomide is 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. The test should ensure the patient is not pregnant when she starts treatment with thalidomide.

Follow-up and end of treatment

A medically supervised pregnancy test should be repeated 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.

Men

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 not using effective contraception.

Prescribing and dispensing restrictions

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.

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

Additional precautions

Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood or semen during therapy or for 1 week following discontinuation of thalidomide.

Educational materials

In order to assist patients in avoiding foetal exposure to thalidomide and to provide additional important safety information, the Marketing Authorisation holder will provide educational material to healthcare professionals. The Thalidomide Celgene Pregnancy Prevention Programme reinforces the warnings about the teratogenicity of thalidomide, provides advice on contraception before therapy is started and provides guidance on the need for pregnancy testing. Full patient information about the teratogenic risk and the pregnancy prevention measures as specified in the Thalidomide Celgene Pregnancy Prevention Programme should be given by the physician to women of childbearing potential and, as appropriate, to male patients.

Amenorrhea

The use of thalidomide could be associated with menstrual disorders including amenorrhea. Amenorrhea during thalidomide therapy should be assumed to result from pregnancy, until it is medically confirmed that the patient is not pregnant. A clear mechanism by which thalidomide can induce amenorrhea is not elucidated. The reported events occurred in young (premenopausal) women (median age 36 years) receiving thalidomide for non multiple myeloma indications, had an onset within 6 months of initiating treatment and reversed upon discontinuation of thalidomide. In documented case reports with hormone evaluation, the event of amenorrhoea was associated with decreased estradiol levels and elevated FSH/LH levels. When provided, antiovary antibodies were negative and prolactin level was within the normal range.

Cardiovascular disorders

Myocardial infarction

Myocardial infarction (MI) has been reported in patients receiving thalidomide, particularly in those with known risk factors. Patients with known risk factors for MI, including prior thrombosis, should be closely monitored and action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

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) (see section 4.8). The risk appears to be greatest during the first 5 months of therapy. Thromboprophylaxis and dosing/anticoagulation therapy recommendations are provided in section 4.2.

Previous history of thromboembolic events or concomitant administration of erythropoietic agents or other agents such as hormone replacement therapy, may also increase thromboembolic 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. Action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension and hyperlipidaemia).

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.

Peripheral neuropathy

Peripheral neuropathy is a very common, potentially severe, adverse reaction to treatment with thalidomide that may result in irreversible damage (see section 4.8). In a phase 3 study, the median time to first neuropathy event was 42.3 weeks.

If the patient experiences peripheral neuropathy, follow the dose and schedule modification instruction provided in section 4.2.

Careful monitoring of patients for symptoms of neuropathy is recommended. Symptoms include paraesthesia, dysaesthesia, discomfort, abnormal co-ordination or weakness.

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 (see section 4.5).

Thalidomide may also potentially aggravate existing neuropathy and should therefore not be used in patients with clinical signs or symptoms of peripheral neuropathy unless the clinical benefits outweigh the risks.

Syncope, bradycardia and atrioventricular block

Patients should be monitored for syncope, bradycardia and atrioventricular block; dose reduction or discontinuation may be required.

Pulmonary hypertension

Cases of pulmonary hypertension, some fatal, have been reported in patients treated with thalidomide. Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating and during thalidomide therapy.

Haematological disorders

Neutropenia

The incidence of neutropenia grade 3 or 4 reported as adverse reactions was higher in multiple myeloma patients receiving MPT (Melphalan, Prednisone, Thalidomide) than in those receiving MP (Melphalan, Prednisone): 42.7 % versus 29.5 % respectively (study IFM 99-06). Adverse reactions from post-marketing experience such as febrile neutropenia and pancytopenia were reported with thalidomide. Patients should be monitored and dose delay, reduction or discontinuation may be required (see section 4.2).

Thrombocytopenia

Thrombocytopenia, including grade 3 or 4 adverse reactions, has been reported in multiple myeloma patients receiving MPT. Patients should be monitored and dose delay, reduction or discontinuation may be required (see section 4.2). Patients and physicians are advised to be observant for signs and symptoms of bleeding including petechiae, epistaxis and gastrointestinal haemorrhage, especially in case of concomitant medication susceptible to induce bleeding (see section 4.8).

Hepatic disorders

Hepatic disorders, mainly abnormal liver test results, were reported. No specific pattern was identified between hepatocellular and cholestatic abnormalities, with some cases having a mixed presentation. The majority of the reactions occurred within the first 2 months of therapy and resolved spontaneously without treatment after thalidomide discontinuation. Patients should be monitored for liver function, particularly in case of pre-existing liver disorder or concomitant use of medication susceptible to induce liver dysfunction (see section 4.8).

Skin reactions

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

Somnolence

Thalidomide frequently causes somnolence. 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 (see section 4.7).

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.

Infections

Patients should be monitored for severe infections including sepsis and septic shock.

Cases of viral reactivation have been reported in patients receiving thalidomide, including serious cases of herpes zoster or hepatitis B virus (HBV) reactivation.

Some of the cases of herpes zoster reactivation resulted in disseminated herpes zoster, requiring a temporary hold of the treatment with thalidomide and adequate antiviral treatment.

Some of the cases of HBV reactivation progressed to acute hepatic failure and resulted in discontinuation of thalidomide. Hepatitis B virus status should be established before initiating treatment with thalidomide. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

Previously infected patients should be closely monitored for signs and symptoms of viral reactivation, including active HBV infection, throughout therapy.

Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)

A statistically significant increase of AML and MDS has been observed in an ongoing clinical study in patients with previously untreated MM receiving the combination of melphalan, prednisone, and thalidomide (MPT). The risk increases over time and was about 2 % after two years and about 4 % after three years. An increased incidence of second primary malignancies (SPM) has also been observed in patients with newly diagnosed MM receiving lenalidomide. Among invasive SPMs, cases of MDS/AML were observed in patients receiving lenalidomide in combination with melphalan or immediately following high dose melphalan and autologous stem cell transplantation.

The benefit achieved with thalidomide and the risk of AML and MDS must be taken into account before initiating treatment with thalidomide in combination with melphalan and prednisone. Physicians should carefully evaluate patients before and during treatment using standard cancer screening and institute treatment as indicated.

Patients with renal or hepatic impairment

Studies conducted in healthy subjects and patients with multiple myeloma suggest that Thalidomide is not influenced to any significant extent by renal or hepatic function (see section 5.2). However, this has not formally been studied in patients with impaired renal or hepatic function; therefore patients with severe renal or hepatic impairment should be carefully monitored for any adverse effects.

Allergic reactions

Cases of allergic reactions/angioedema have been reported. Thalidomide should be discontinued if a skin rash occurs and only resumed following appropriate clinical evaluation. If angioedema occurs, use of thalidomide should not be resumed.

4.5 Interaction with other medicinal products and other forms of interaction

Thalidomide is a poor substrate for cytochrome P450 isoenzymes and therefore clinically important interactions with medicinal products that are inhibitors and/or inducers of this enzyme system are unlikely. Non-enzymatic hydrolysis of thalidomide, being the primary clearance mechanism, suggests that the potential for drug-drug interactions with thalidomide is low.

Increase of sedative effects of other medicinal products

Thalidomide has sedative properties thus may enhance the sedation induced by anxiolytics, hypnotics, antipsychotics, H₁ anti-histamines, opiate derivatives, barbiturates and alcohol. Caution should be used when thalidomide is given in combination with medicinal products that cause drowsiness.

Bradycardic effect

Due to thalidomide's potential to induce bradycardia, caution should be exercised with medicinal products having the same pharmacodynamic effect such as active substances known to induce torsade de pointes, beta blockers or anticholinesterase agents.

Medicinal products known to cause peripheral neuropathy

Medicinal products known to be associated with peripheral neuropathy (e.g. vincristine and bortezomib) should be used with caution in patients receiving thalidomide.

Hormonal contraceptives

Thalidomide does not interact with hormonal contraceptives. In 10 healthy women, the pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of a single dose containing 1.0 mg of norethindrone acetate and 0.75 mg of ethinyl estradiol were studied. The results were similar with and without co-administration of thalidomide 200 mg/day to steady-state levels. However, combined hormonal contraceptives are not recommended due to the increased risk of venous thrombo-embolic disease.

Warfarin

Multiple dose administration of 200 mg thalidomide q.d. for 4 days had no effect on the international normalized ratio (INR) in healthy volunteers. However, due to the increased risk of thrombosis in cancer patients, and a potentially accelerated metabolism of warfarin with corticosteroids, close monitoring of INR values is advised during thalidomide-prednisone combination treatment as well as during the first weeks after ending these treatments.

Digoxin

Thalidomide does not interact with digoxin. In 18 healthy male volunteers, multiple dose administration of 200 mg thalidomide had no apparent effect on the single dose pharmacokinetics of digoxin. In addition, single dose administration of 0.5 mg digoxin had no apparent effect on thalidomide pharmacokinetics. It is not known whether the effect will be different in multiple myeloma patients.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential must use one effective method of contraception for 4 weeks before therapy, during therapy, and during 4 weeks after thalidomide therapy (see section 4.4). If pregnancy occurs in a woman treated with thalidomide, treatment must be stopped immediately and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice.

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 when having sexual intercourse with a pregnant woman or with a woman of childbearing potential who is not using effective contraception.

If pregnancy occurs in a partner of a male patient taking thalidomide, the female partner should be referred to a physician specialised or experienced in teratology for evaluation and advice.

Pregnancy

Thalidomide is contraindicated during pregnancy and in women of childbearing potential unless all the conditions of the Thalidomide Celgene Pregnancy Prevention Programme are met (see section 4.3)

Thalidomide is a powerful human teratogen, inducing a high frequency (about 30 %) of severe and live-threatening birth defects such as: ectromelia (amelia, phocomelia, hemimelia) of the upper and/or lower extremities, microtia with abnormality of the external acoustic meatus (blind or absent), middle and internal ear lesions (less frequent), ocular lesions (anophthalmia, microphthalmia), congenital heart disease, renal abnormalities. Other less frequent abnormalities have also been described.

Breast feeding

It is unknown whether thalidomide is excreted in human breast milk. Animal studies have shown excretion of thalidomide in breast milk. Therefore breast-feeding should be discontinued during therapy with thalidomide.

Fertility

A study in rabbits demonstrated no effect on fertility indices in males or females although testicular degeneration was observed in males.

4.7 Effects on ability to drive and use machines

Thalidomide Celgene has minor or moderate influence on the ability to drive and use machines.

Thalidomide may cause fatigue, dizziness, somnolence and blurred vision (see section 4.8). If affected, patients should be instructed not to drive cars, use machines or perform hazardous tasks while being treated with thalidomide.

4.8 Undesirable effects

Summary of the safety profile

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.

In addition to the adverse reactions outlined above, thalidomide in combination with dexamethasone in other clinical studies led to the very common adverse reaction of fatigue; common adverse reactions of transient ischaemic event, syncope, vertigo, hypotension, mood altered, anxiety, blurred vision, nausea and dyspepsia; and uncommon adverse reactions of cerebrovascular accident, diverticular perforation, peritonitis, orthostatic hypotension and bronchitis.

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

Tabulated list of adverse reactions

Table 3 contains only the adverse reactions for which a causal relationship with medicinal product treatment could reasonably be established. Frequencies given are based on the observations during a pivotal comparative clinical study investigating the effect of thalidomide in combination with melphalan and prednisone in previously untreated multiple myeloma patients. In addition to the adverse reactions noted in the pivotal study, adverse reactions based on post-marketing experience with the medicinal product are provided after Table 3.

Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1000$); very rare ($< 1/10,000$) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: Frequency of adverse drug reactions (ADRs) with thalidomide in combination with melphalan and prednisone

System Organ Class	All ADRs
Infections and infestations	<u>Common</u> Pneumonia
Blood and lymphatic system disorders	<u>Very Common</u> Neutropenia Leukopenia Anaemia Lymphopenia Thrombocytopenia
Psychiatric disorders	<u>Common</u> Confusional state Depression
Nervous system disorders	<u>Very Common</u> Peripheral neuropathy* Tremor Dizziness Paraesthesia Dysaesthesia Somnolence <u>Common</u> Abnormal coordination
Cardiac disorders	<u>Common</u> Cardiac failure Bradycardia
Vascular disorders	<u>Common</u> Deep vein thrombosis*
Respiratory, thoracic and mediastinal disorders	<u>Common</u> Pulmonary embolism* Interstitial lung disease Bronchopneumopathy Dyspnea

Gastrointestinal disorders	<u>Very Common</u> Constipation <u>Common</u> Vomiting Dry mouth
Skin and subcutaneous tissue disorders	<u>Common</u> Toxic skin eruption Rash Dry skin
General disorders and administration site conditions	<u>Very Common</u> Peripheral oedema <u>Common</u> Pyrexia Asthenia Malaise

* see section 4.8 description of selected adverse reactions

Additional adverse reactions related to post-marketing experience with thalidomide and not seen in the pivotal study include: toxic epidermal necrolysis (see section 4.4), intestinal obstruction, hypothyroidism, sexual dysfunction, tumour lysis syndrome (see section 4.4), gastro-intestinal perforations, allergic reactions (hypersensitivity, angioedema/urticaria) (see section 4.4), hearing impaired or deafness, renal failure, myocardial infarction (see section 4.4), worsening of Parkinson's disease symptoms, severe infections (e.g. fatal sepsis including septic shock) (see section 4.4), convulsions, atrial fibrillation, atrioventricular block (see section 4.4), menstrual disorders including amenorrhea (see section 4.4), pancreatitis, gastrointestinal haemorrhage (see section 4.4), hepatic disorders (see section 4.4), posterior reversible encephalopathy syndrome (PRES), pulmonary hypertension (see section 4.4) and viral infections, including herpes zoster and hepatitis B virus reactivation (see section 4.4).

Description of selected adverse reactions

Blood and lymphatic system disorders

Adverse reactions for haematological disorders are provided compared to the comparator arm, as the comparator has a significant effect on these disorders (Table 4).

Table 4: Comparison of haematological disorders for the melphalan, prednisone (MP) and melphalan, prednisone, thalidomide (MPT) combinations in study IFM 99-06 (see section 5.1)

	n (% of patients)	
	MP (n=193)	MPT (n=124)
	Grades 3 and 4*	
Neutropenia	57 (29.5)	53 (42.7)
Leukopenia	32 (16.6)	32 (25.8)
Anaemia	28 (14.5)	17 (13.7)
Lymphopenia	14 (7.3)	15 (12.1)
Thrombocytopenia	19 (9.8)	14 (11.3)

* WHO Criteria

Additional adverse reactions from post-marketing experience with thalidomide and not seen in the pivotal study include febrile neutropenia and pancytopenia.

Teratogenicity

The risk of intra-uterine death or severe birth defects, primarily phocomelia, is extremely high. Thalidomide must not be used at any time during pregnancy (see sections 4.4 and 4.6).

Venous and arterial thromboembolic events

An increased risk of venous thromboembolism (such as deep vein thrombosis and pulmonary embolism) and arterial thromboembolism (such as myocardial infarction and cerebrovascular event) has been reported in patients treated with thalidomide (see section 4.4).

Peripheral neuropathy

Peripheral neuropathy is a very common, potentially severe, adverse reaction of treatment with thalidomide that may result in irreversible damage (see section 4.4). Peripheral neuropathy generally occurs following chronic use over a period of months. However, reports following relatively short-term use also exist. Incidence of neuropathy events leading to discontinuation, dose reduction or interruption increases with cumulative dose and duration of therapy. Symptoms may occur some time after thalidomide treatment has been stopped and may resolve slowly or not at all.

Posterior reversible encephalopathy syndrome (PRES)/ Reversible posterior leukoencephalopathy syndrome (RPLS)

Cases of PRES/ RPLS have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The majority of the reported cases had recognized risk factors for PRES/RPLS, including hypertension, renal impairment and concomitant use of high dose corticosteroids and/or chemotherapy.

Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)

AML and MDS have been reported in an ongoing clinical study in patients with previously untreated multiple myeloma receiving the combination of melphalan, prednisone, and thalidomide (see section 4.4).

Elderly population

The adverse reaction profile reported in patients > 75 years of age treated with thalidomide 100 mg once daily was similar to the adverse reaction profile observed in patients ≤ 75 years of age treated with thalidomide 200 mg once daily (see Table 3). However, patients with age > 75 years are potentially at risk for a higher frequency of serious adverse reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Eighteen cases of overdose have been reported in the literature concerning doses up to 14.4 g. No fatalities have been reported and all overdose patients recovered without sequelae. There is no specific antidote for a thalidomide overdose. In the event of an overdose, the patient's vital signs should be monitored and appropriate supportive care given to maintain blood pressure and respiratory status.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressants, other immunosuppressants, ATC code: L04AX02.

Thalidomide has a chiral centre and is used clinically as a racemate of (+)-(R)- and (-)-(S)-thalidomide. The spectrum of activity of thalidomide is not fully characterised.

Mechanism of action

Thalidomide shows immunomodulatory anti-inflammatory and potential anti-neoplastic activities. Data from *in vitro* studies and clinical trials suggest that the immunomodulatory, anti-inflammatory and anti-neoplastic effects of thalidomide may be related to suppression of excessive tumour necrosis factor-alpha (TNF- α) production, down-modulation of selected cell surface adhesion molecules

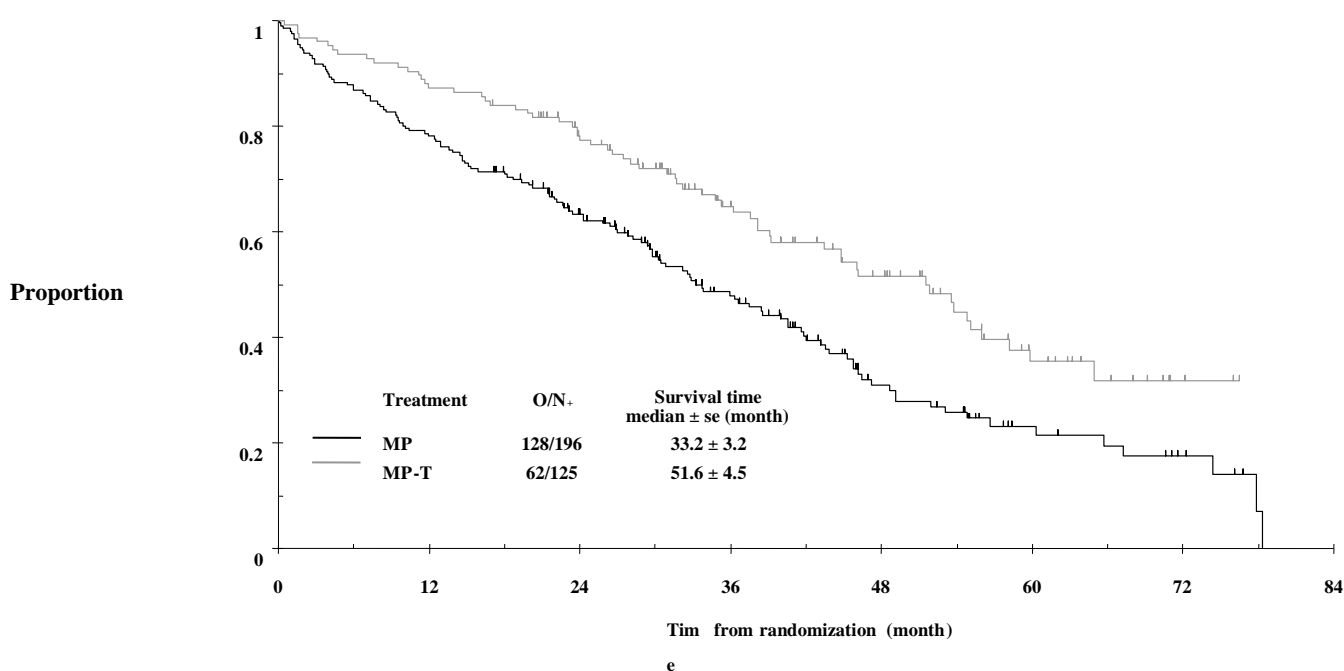
involved in leukocyte migration and anti-angiogenic activity. Thalidomide is also a non-barbiturate centrally active hypnotic sedative. It has no anti-bacterial effects.

Clinical efficacy and safety

Results from IFM 99-06, a Phase 3, randomised, open label, parallel group, multicentre study have demonstrated a survival advantage when thalidomide is used in combination with melphalan and prednisone for 12 cycles of 6 weeks in the treatment of newly diagnosed multiple myeloma patients. In this study the age range of patients was 65-75 years, with 41 % (183/447) of patients 70 years old or older. The median dose of thalidomide was 217 mg and > 40 % of patients received 9 cycles. Melphalan and prednisone were dosed at 0.25 mg/kg/day and 2 mg/kg/day respectively on days 1 to 4 of each 6 weeks cycle.

Further to the per protocol analysis, an update was conducted for the IFM 99-06 study providing an additional 15 months follow-up data. The median overall survival (OS) was 51.6 ± 4.5 and 33.2 ± 3.2 months in the MPT and MP groups, respectively (97.5 % CI 0.42 to 0.84). This 18 month difference was statistically significant with a hazard ratio of reduction of risk of death in the MPT arm of 0.59, 97.5 % confidence interval of 0.42-0.84 and p-value of < 0.001 (see Figure 1).

Figure 1: Overall survival according to treatment



Paediatric Population

The European Medicines Agency has waived the obligation to submit the results of studies with thalidomide in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Absorption of thalidomide is slow after oral administration. The maximum plasma concentrations are reached 1-5 hours after administration. Co-administration of food delayed absorption but did not alter the overall extent of absorption.

Distribution

The plasma protein binding of the (+)-(R) and (-)-(S) enantiomers was found to be 55 % and 65 % respectively. Thalidomide is present in the semen of male patients at levels similar to plasma concentrations. Therefore, because of the known severe teratogenic effects of the product, during treatment with thalidomide and for 1 week after stopping the treatment, male patients must use condoms if their partner is pregnant or is of childbearing potential not using effective contraception (see section 4.4). The distribution of thalidomide is not influenced by age, gender, renal function and blood chemistry variables, to any significant level.

Biotransformation

Thalidomide is metabolised almost exclusively by non-enzymatic hydrolysis. In plasma, unchanged thalidomide represents 80 % of the circulatory components. Unchanged thalidomide was a minor component (< 3 % of the dose) in urine. In addition to thalidomide, hydrolytic products N-(o-carboxybenzoyl) glutarimide and phthaloyl isoglutamine formed via non-enzymatic processes are also present in plasma and in majority in urine. Oxidative metabolism does not contribute significantly to the overall metabolism of thalidomide. There is minimal cytochrome P450 catalysed hepatic metabolism of thalidomide. There are *in vitro* data indicating that prednisone may give rise to enzyme induction which could reduce the systemic exposure of concomitantly used medicinal products. The *in vivo* relevance of these findings is unknown.

Elimination

The mean elimination half-life of thalidomide in plasma following single oral doses between 50 mg and 400 mg was 5.5 to 7.3 hours. Following a single oral dose of 400 mg of radio-labelled thalidomide, the total mean recovery was 93.6 % of the administered dose by day 8. The majority of the radioactive dose was excreted within 48 hour following dose administration. The major route of excretion was via the urine (> 90 %) while faecal excretion was minor.

There is a linear relationship between body weight and estimated thalidomide clearance; in multiple myeloma patients with body weight from 47-133 kg, thalidomide clearance ranged from approximately 6-12 L/h, representing an increase in thalidomide clearance of 0.621 L/h per 10 kg body weight increase.

Linearity/ non linearity

Total systemic exposure (AUC) is proportional to dose at single-dose conditions. No time dependency of the pharmacokinetics has been observed.

Hepatic and renal impairment

The extent of thalidomide metabolism by the liver cytochrome P450 system is minimal and intact thalidomide is not excreted by the kidney. Measures of renal function (CL_{Cr}) and liver function (blood chemistry) indicate minimal effect of kidney and liver function on the pharmacokinetics of thalidomide. As such the metabolism of thalidomide is not expected to be affected by hepatic or renal dysfunction. Data from patients with end-stage renal disease suggest no impact of kidney function on thalidomide pharmacokinetics. However, considering that pharmacologically active metabolites are eliminated via urine, it is advised that patients with severe renal impairment should be carefully monitored for any adverse reactions.

5.3 Preclinical safety data

In the male dog, after one year of dosing, reversible bile plugs in canaliculi were observed at exposures greater than 1.9 fold the human exposure.

Decreased platelet counts were noted in the mouse and rat studies. The latter appears to be related to thalidomide and occurred at exposures greater than 2.4 fold the human exposure. This decrease did not result in clinical signs.

In a one-year dog study, enlarged and/or blue discoloration of mammary glands and prolonged estrus were observed in females at exposures equal to 1.8 or greater than 3.6-fold the human exposure, respectively. The relevance to humans is unknown.

The effect of thalidomide on thyroid function was assessed in both rats and dogs. No effects were observed in dogs; however in rats, there was an apparent dose-dependent decrease in total and free T4 that was more consistent in the female.

No mutagenic or genotoxic effect has been revealed when thalidomide was assayed in a standard battery of genotoxicity tests. No evidence of carcinogenicity was observed at exposures approximately 15, 13 and 39 times the estimated clinical AUC at the recommended starting dose in mice, male rats and female rats respectively.

Animal studies have demonstrated differences in species susceptibility to the teratogenic effects of thalidomide. In humans, thalidomide is a proven teratogen.

A study in rabbits demonstrated no effect on fertility indices in males or females although testicular degeneration was observed in males.

A peri and postnatal toxicity study performed in rabbits with thalidomide administered at doses up to 500 mg/kg/day resulted in abortions, increased stillbirths and decreased pup viability during lactation. Pups from mothers treated with thalidomide had increased abortions, reduced body weight gain, alterations in learning and memory, decreased fertility, and reduced pregnancy index.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Pregelatinized starch
Magnesium stearate

Capsule shell

Gelatin
Titanium dioxide (E171)

Printing ink

Shellac
Black iron oxide (E172)
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/ PCTFE /aluminium blister containing 14 capsules.

Pack sizes: 28 capsules (two blisters) in a wallet card.

6.6 Special precautions for disposal and other handling

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.

All unused capsules should be returned to the pharmacist at the end of treatment.

7. MARKETING AUTHORISATION HOLDER

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/443/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 April 2008
Date of latest renewal: 18 December 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency: <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER (S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Penn Pharmaceutical Services Limited
Tafarnaubach Industrial Estate
Tredegar
Gwent
NP22 3AA
United Kingdom

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription.(see Annex 1: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports (PSUR)**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web- portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

1. The MAH shall agree the details of a controlled distribution system with the National Competent Authorities and must implement such programme nationally to ensure that:
 - Prior to launch, all doctors and pharmacists who intend to prescribe or dispense Thalidomide Celgene receive a Dear Healthcare Professional letter as described below.
 - Prior to prescribing all healthcare professionals who intend to prescribe (and in agreement with the National Competent Authority, dispense) Thalidomide Celgene are provided with an Educational Healthcare Professional's Kit containing the following:
 - Healthcare professional booklet
 - Patient booklets
 - Patient cards
 - Summary of Product Characteristics, Package Leaflet and Labelling
2. The MAH shall implement a Pregnancy Prevention Programme (PPP) in each Member State. Details of the PPP should be agreed with the National Competent Authorities in each Member State and put in place prior to the marketing of the medicinal product.
3. The MAH should agree the final text of the Dear Healthcare Professional letter and the contents of the Educational Healthcare Professional's Kit with the National Competent Authority in each Member State prior to marketing of the product and ensure that the materials contain the key elements as described below.
4. The MAH should agree on the implementation of the patient card system in each Member State.
5. The MAH should ensure that the educational materials are provided to and reviewed by the national patients' organisations or if such an organisation does not exist or can not be involved, by a relevant patients group. Patients involved should be preferably naïve to the history of thalidomide. Results of the user testing will have to be provided to the national competent authority and final materials validated at a national level.
6. The MAH should also agree with each Member State prior to the launch of the product:
 - The most appropriate strategies to monitor the off label use within national territories
 - The collection of detailed data with at least patient demographics and indication in order to monitor closely the off-label use within national territory
 - The set-up of national measures to assess the effectiveness of and compliance with the PPP.
7. The MAH shall notify the EMA and the appropriate national patients and victims representatives of the proposed launch date before launch in each Member State.
8. The MAH should distribute in Member States where Thalidomide Celgene is in use a Direct Healthcare Professional Communication letter informing healthcare professionals of the risk of second primary malignancies (SPM) in patients treated with Thalidomide Celgene, in accordance with its communication plan.

Key elements to be included

Dear Healthcare Professional letter

The Dear Healthcare Professional letter will consist of two parts:

- Core text as agreed by the CHMP
- National specific requirements agreed with the National Competent Authority regarding:
 - Distribution of the product
 - Procedures to ensure that all appropriate measures have been performed prior to thalidomide being dispensed

Educational healthcare professional's kit

The educational healthcare professional's kit shall contain the following elements:

- Healthcare professional booklet
 - History of thalidomide, background on Thalidomide Celgene and its licensed indication
 - Posology
 - Maximum duration of prescription
 - 4 weeks for women with childbearing potential
 - 12 weeks for men and women without childbearing potential
 - Teratogenicity and the need to avoid foetal exposure
 - Obligations of healthcare professionals who intend to prescribe or dispense Thalidomide Celgene including
 - The need to provide comprehensive advice and counselling to patients
 - That patients should be capable of complying with the requirements for the safe use of thalidomide
 - Need to provide patients with the appropriate patient educational material
 - Report any pregnancy, neuropathy or other adverse events to Celgene and the local health authority (if applicable to a Member State) using the forms provided in the "Educational Healthcare Professional's Kit"
 - Safety advice relevant to all patients
 - Description and management of venous and arterial thromboembolic events, cardiovascular events (such as ischaemic heart disease, myocardial infarction, and bradycardia and syncope), peripheral neuropathy, severe skin reactions, and somnolence
 - Disposal of unwanted medicine
 - Not to donate blood during treatment and for one week after treatment ends
 - Algorithm for Pregnancy Prevention Plan implementation
 - This shall assist with patient categorisation, and determination of required pregnancy prevention and testing measures.
 - Pregnancy Prevention Programme information
 - Definition of women of childbearing potential (WCBP) and actions the prescriber should take if childbearing status is unclear
 - Information on what is effective contraception
 - Safety advice for WCBP
 - Need to avoid foetal exposure
 - Pregnancy prevention requirement, definition and need for adequate contraceptive methods
 - That if she needs to change or stop using her method of contraception she should inform:
 - the physician prescribing her contraception that she is on thalidomide
 - the physician prescribing thalidomide that she has stopped or changed her method of contraception
 - Pregnancy testing requirements
 - Advice on suitable tests
 - Frequency (before commencing, monthly during treatment and after finishing treatment)
 - Need to stop Thalidomide Celgene immediately upon suspicion of pregnancy
 - Need to tell treating doctor immediately upon suspicion of pregnancy
 - Safety advice for men
 - The need to avoid foetal exposure
 - That thalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a women with childbearing potential not using effective contraception

- That if his partner becomes pregnant he should inform his treating doctor immediately and always use a condom during intercourse
 - That he should not donate semen during therapy and for one week after discontinuation of thalidomide
- Pregnancy reporting requirements
 - Stop Thalidomide Celgene immediately upon suspicion of pregnancy
 - Refer patient to physician specialised or experienced in dealing with teratology for advice and evaluation
 - Complete pregnancy reporting form as provided in the “Educational Healthcare Professional’s Kit”
 - Local contact details for reporting of any suspected pregnancy
- Pregnancy initial and outcome reporting forms
 - Post-marketing and compliance assessment (as applicable to a Member State)
 - Neuropathy and adverse reaction reporting forms
- Treatment initiation forms
 - There should be 3 types of treatment initiation forms:
 - Female patient of childbearing potential
 - Female patient of non-childbearing potential
 - Male patient
 - All Treatment Initiation Forms should contain the following elements:
 - Teratogenicity warning
 - Date of counselling
 - Affirmation of patient understanding regarding the risk of thalidomide and the PPP measures
 - Patient details, signature and date
 - Prescriber name, signature and date
 - Aim of this document i.e. as stated in the PPP: “The aim of the treatment initiation form is to protect patients and any possible foetuses by ensuring that patients are fully informed of and understand the risk of teratogenicity and other adverse reactions associated with the use of thalidomide. It is not a contract and does not absolve anybody from his/her responsibilities with regard to the safe use of the product and prevention of foetal exposure.”
 - Treatment initiation forms for female patients with childbearing potential should also include:
 - Confirmation that the physician has discussed the following:
 - The need to avoid foetal exposure
 - That if she is pregnant or plans to be, she must not take Thalidomide Celgene
 - The need for effective contraception, without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment, and 4 weeks after the end of treatment
 - That if she needs to change or stop using her method of contraception she should inform:
 - the physician prescribing her contraception that she is on thalidomide
 - the physician prescribing thalidomide that she has stopped or changed her method of contraception
 - The need for pregnancy tests i.e. before treatment, every 4 weeks during treatment and after treatment
 - The need to stop Thalidomide Celgene immediately upon suspicion of pregnancy
 - The need to contact their doctor immediately upon suspicion of pregnancy

- That she should not share the treatment with any other person
 - That she should not donate blood during therapy and for one week following discontinuation of thalidomide
 - That she should return the capsules to the pharmacist at the end of treatment
- Treatment initiation forms for female patients with no childbearing potential should also include:
 - Confirmation that the physician has discussed the following:
 - That she should not share the treatment with any other person
 - That she should not donate blood during therapy and for one week following discontinuation of thalidomide
 - That she should return the capsules to the pharmacist at the end of treatment
- Treatment initiation forms for male patients should also include:
 - Confirmation that the physician has discussed the following:
 - The need to avoid foetal exposure
 - That thalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a women with childbearing potential not on effective contraception
 - That if his partner becomes pregnant he should inform his treating doctor immediately and always use a condom
 - That he should not donate blood or semen during therapy and for one week following discontinuation of thalidomide
 - That he should not share the treatment with any other person
 - That he should return the capsules to the pharmacist at the end of treatment
- Patient cards and/or equivalent tools:
 - verification that appropriate counselling has taken place
 - documentation of childbearing potential status
 - check box (or similar) which physician ticks to confirm that patient is using effective contraception (if female with childbearing potential)
 - verification of initial negative pregnancy test prior to start of treatment (if female with childbearing potential)
 - pregnancy test dates and results
- Educational patient booklets:
 - The booklets can be of 3 types or a single patient booklet that combines the information for each patient category:
 - Booklet for women of childbearing potential and their partners
 - Booklet for women patients who are not of childbearing potential
 - Booklet for male patients
 - All booklets should contain the following information
 - That Thalidomide Celgene is teratogenic
 - That Thalidomide Celgene may cause venous and arterial thromboembolism, cardiovascular events (such as ischaemic heart disease, myocardial infarction, and bradycardia and syncope), peripheral neuropathy, severe skin reactions, and somnolence
 - Description of the patient card and its use in the individual Member State
 - Guidance on handling Thalidomide Celgene for patients, caregivers and family members
 - National or other applicable specific arrangements for a prescription for thalidomide to be dispensed
 - That Thalidomide Celgene must not be given to any other person
 - That the patient should not donate blood
 - That the patient should tell their doctor about any adverse events

- That any unused capsules should be returned to the pharmacist at the end of the treatment
- The following information should also be provided in the appropriate booklets:
 - Female patient of childbearing potential
 - The need to avoid foetal exposure
 - The need for effective contraception
 - That if she needs to change or stop using her method of contraception she should inform:
 - the physician prescribing her contraception that she is on thalidomide
 - the physician prescribing thalidomide that she has stopped or changed her method of contraception
 - The need for pregnancy tests i.e. before treatment, every 4 weeks during treatment and after treatment
 - The need to stop Thalidomide Celgene immediately upon suspicion of pregnancy
 - The need to contact their doctor immediately upon suspicion of pregnancy
 - Male patients
 - The need to avoid foetal exposure
 - That thalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a women with childbearing potential not on effective contraception
 - That if his partner becomes pregnant he should inform his treating doctor immediately and always use a condom
 - That he should not donate semen during therapy and for one week following discontinuation of thalidomide

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

WALLET CARD

1. NAME OF THE MEDICINAL PRODUCT

Thalidomide Celgene 50 mg hard capsules
Thalidomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 50 mg of thalidomide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only as directed by your doctor.

WARNING: Thalidomide causes birth defects and foetal death.

Patients must follow the Thalidomide Celgene Pregnancy Prevention Programme.

KEEP THE PACKAGE INTACT

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Unused medicinal product should be returned to your pharmacist.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/443/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Thalidomide Celgene 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Thalidomide Celgene 50 mg
Thalidomide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Thalidomide Celgene 50 mg hard capsules Thalidomide

WARNING

Thalidomide causes birth defects and foetal death. Do not take thalidomide if you are pregnant or could become pregnant. You must follow the contraception advice given to you by your doctor.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist or nurse.
- **This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.**
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Thalidomide Celgene is and what it is used for
2. What you need to know before you take Thalidomide Celgene
3. How to take Thalidomide Celgene
4. Possible side effects
5. How to store Thalidomide Celgene
6. Contents of the pack and other information

1. What Thalidomide Celgene is and what it is used for

What Thalidomide Celgene is

Thalidomide Celgene contains an active substance called thalidomide. This belongs to a group of medicines which affect how your immune system works.

What Thalidomide Celgene is used for

Thalidomide Celgene is used with two other medicines called ‘melphalan’ and ‘prednisone’ to treat adults aged 65 years and over, with a type of cancer called multiple myeloma. It is used in people who have recently been diagnosed and who have not been prescribed another medicine for their multiple myeloma before, or who cannot be treated with high dose chemotherapy, which can be very difficult for the body to handle.

What is multiple myeloma

Multiple myeloma is a type of cancer which affects a certain type of white blood cell, called the plasma cell. These cells collect in the bone marrow and divide out of control. This can damage the bone and kidneys. Multiple myeloma generally cannot be cured. However, the signs and symptoms can be greatly reduced or disappear for a period of time. This is called a ‘remission’.

How Thalidomide Celgene works

Thalidomide Celgene works by helping the body’s immune system and directly attacking the cancer. It works in a number of different ways:

- by stopping the cancer cells developing
- by stopping blood vessels growing in the cancer
- by stimulating part of the immune system to attack the cancer cells.

2. What you need to know before you take Thalidomide Celgene

You will have been given specific instructions by your doctor, particularly on the effects of thalidomide on unborn babies (outlined in the Thalidomide Celgene Pregnancy Prevention Programme).

You will have been given a patient card or any other relevant document by your doctor. Read it carefully and follow the related instructions.

If you do not fully understand these instructions, please ask your doctor to explain them again before you take thalidomide. See also further information in this section under “Warnings and precautions” and “Pregnancy and breast-feeding”.

Do not take Thalidomide Celgene

- if you are pregnant or think you may be pregnant or are planning to become pregnant, **as Thalidomide Celgene causes birth defects and foetal death.**
- if you are able to become pregnant, unless you follow all the necessary measures to prevent you from becoming pregnant (see section 2 “Warnings and precautions” and “Pregnancy and breast-feeding”).
- if you are able to become pregnant, your doctor will record with each prescription that the necessary measures have been taken and will provide you with this confirmation.
- if you are allergic to thalidomide or any of the other ingredients of this medicine listed in section 6 “Content of the pack and other information”.

Do not take Thalidomide Celgene if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Thalidomide Celgene.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking this medicine in the following situations:

For women taking Thalidomide Celgene

Before starting the treatment, you should ask your doctor if you are able to become pregnant, even if you think this is unlikely.

If you are able to become pregnant:

- Your doctor will make sure that you have pregnancy tests
 - before treatment
 - every 4 weeks during treatment
 - 4 weeks after stopping treatment
- You must use one effective method of contraception:
 - for 4 weeks before starting treatment
 - during treatment
 - until 4 weeks after stopping treatment

Your doctor will tell you what method of contraception to use.

If you are able to become pregnant, your doctor will record with each prescription that the necessary measures, as outlined above, have been taken and will give you a record of this on your patient card or any other relevant documents.

For men taking Thalidomide Celgene

Thalidomide passes into semen. Therefore do not have unprotected intercourse.

- Pregnancy and any exposure during pregnancy must be avoided. Always use a condom:
 - during treatment
 - for 1 week after stopping treatment
- You must not donate semen:
 - during treatment
 - for 1 week after stopping treatment

For all patients

Talk to your doctor before taking Thalidomide Celgene if

- you have had a heart attack, have ever had a blood clot in the past, or if you smoke, have high blood pressure or high cholesterol levels. During the treatment with Thalidomide Celgene you have an increased risk of developing blood clots in the veins and arteries.
- you experienced or have existing slow heart rate (this may be symptoms of bradycardia).
- you have experienced or have existing neuropathy i.e. tingling, abnormal co-ordination or pain in your hands or feet.
- you have experienced sleepiness.
- you have a high total amount of tumour throughout the body, including your bone marrow. This could lead to a condition where the tumours break down and cause unusual levels of chemicals in the body which can lead to kidneys failure (this condition is called Tumour Lysis Syndrome).
- you have experienced fever, chills and severe shaking, and possibly complicated by low blood pressure and confusion (these may be symptoms of severe infections).
- you have had an allergic reaction whilst taking thalidomide such as rash, itching, swelling, dizziness or trouble breathing.
- you do not understand the contraception advice given to you by your doctor or if you do not feel able to follow this advice.
- you have high blood pressure from the heart to the lungs.
- you have or have ever had previous viral infection, particularly varicella zona, hepatitis B infection, or HIV. If you are in doubt, talk to your doctor. Treatment with thalidomide may cause virus to become active again in patients who carry it, resulting in a recurrence of the infection. Your doctor should check whether you have ever had hepatitis B infection.

You must not donate blood during Thalidomide Celgene treatment and for 1 week after stopping treatment.

If you are not sure if any of the above apply to you, talk to your doctor before taking Thalidomide Celgene.

Children and adolescents

Thalidomide Celgene is not recommended for use in children and young people under 18 years.

Other medicines and Thalidomide Celgene

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, including herbal medicines.

Make sure you tell your doctor if you are taking any medicines which:

- cause sleepiness as thalidomide may increase their effects. This includes sedatives (such as anxiolytics, hypnotics, antipsychotics, H₁ anti-histamines, opiate derivatives and barbiturates).
- slow the heart rate (induce bradycardia, such as anti-cholinesterases and beta blockers).
- are used for heart problems and complications (such as digoxin), or for thinning the blood (such as warfarin).
- are other treatments for cancer.
- are used for contraception.

Thalidomide Celgene with food, drink and alcohol

Thalidomide Celgene can be taken with or without food (see section 3, “How to take Thalidomide Celgene”).

Do not drink alcohol while you are taking Thalidomide Celgene. This is because alcohol can make you sleepy and Thalidomide Celgene can make you even sleepier.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

Thalidomide causes severe birth defects or death to an unborn baby.

- As little as one capsule taken by a pregnant woman can cause a baby to have serious birth defects.
- These defects can include shortened arms or legs, malformed hands or feet, eye or ear defects, and problems with internal organs.

If you are pregnant, you must not take Thalidomide Celgene. In addition, you must not become pregnant while taking Thalidomide Celgene.

You must use one effective method of contraception if you are a woman who is able to become pregnant (see section 2, “What you need to know before you take Thalidomide Celgene”).

You must stop treatment and inform your doctor straight away if:

- You miss or think you have missed a period, or you have unusual menstrual bleeding, or suspect you are pregnant.
- You have heterosexual intercourse without using an effective method of contraception.

If you do become pregnant during the treatment with thalidomide, you must stop the treatment and inform your doctor immediately.

For men taking Thalidomide Celgene who have a female partner who is able to become pregnant, please see section 2 “What you need to know before you take Thalidomide Celgene”. If your partner becomes pregnant whilst you are taking thalidomide, you should inform your doctor immediately.

Breast-feeding

Do not breastfeed when taking Thalidomide Celgene as it is not known if thalidomide is passed into human breast milk.

Driving and using machines

Do not drive or use any tools or machines if you experience side effects, such as dizziness, tiredness, sleepiness or blurred vision.

3. How to take Thalidomide Celgene

Always take Thalidomide Celgene exactly as your doctor or pharmacist has told you to. Check with your doctor or pharmacist if you are not sure.

How much to take

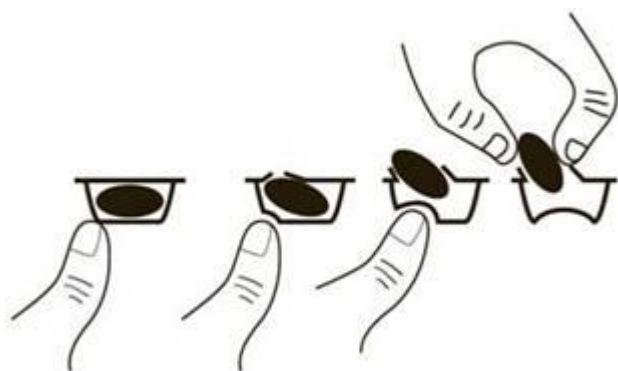
The recommended dose is 200 mg (4 x 50 mg capsules) a day for adults aged 75 years and under or 100 mg (2 x 50 mg capsules) a day for adults aged over 75 years. However your doctor will choose the dose for you, monitor your progress and may adjust your dose. Your doctor will tell you how to take Thalidomide Celgene and for how long you will need to take it (see section 2, “What you need to know before you take Thalidomide Celgene”).

Thalidomide Celgene is taken daily in treatment cycles, each cycle lasting 6 weeks, in combination with melphalan and prednisone which are taken on days 1 to 4 of each 6 week cycle.

Taking this medicine

- Do not break, open or chew the capsules. If powder from a broken Thalidomide Celgene capsule makes contact with the skin, wash the skin immediately and thoroughly with soap and water.
- Take this medicine by mouth.
- Swallow the capsules whole with a full glass of water.
- Do not crush or chew.
- Take the capsules as a single dose before going to bed. This will make you less likely to feel sleepy at other times.

To remove the capsule from the blister, press only one end of the capsule out to push it through the foil. Do not apply pressure on the centre of the capsule as this can cause it to break.



If you take more Thalidomide Celgene than you should

If you take more Thalidomide Celgene than you should, talk to a doctor or go to a hospital straightaway. If possible, take the medicine pack and this leaflet with you.

If you forget to take Thalidomide Celgene

If you forget to take Thalidomide Celgene at your regular time and

- less than 12 hours have passed: take your capsules immediately.
- more than 12 hours have passed: do not take your capsules. Take your next capsules at the usual time the next day.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects although not everybody gets them.

The following side effects may happen with this medicine:

Stop taking Thalidomide Celgene and see a doctor straight away if you notice the following serious side effects – you may need urgent medical treatment:

- Severe skin reactions including rashes, which is a common side effect and blistering of the skin and mucosa (Stevens Johnson Syndrome and toxic epidermal necrolysis, which are rare side effects). You may have a high temperature (fever) at the same time.

Tell your doctor straight away if you notice any of the following serious side effects:

- **Numbness, tingling, abnormal co-ordination or pain in your hands and feet.**
This may be due to nerve damage (called ‘peripheral neuropathy’), which is a very common side effect. It may become very severe, painful and disabling. If you experience such symptoms, speak to your doctor straight away, who may reduce the dose or discontinue the treatment. This side effect usually happens after you have been taking this medicine for several months but can happen sooner than this. It can also happen sometime after treatment has stopped. It may not go away, or may go away slowly.
- **Sudden pain in your chest or difficulty in breathing.**
This may be due to blood clots in the arteries leading to your lungs (called ‘pulmonary embolism’), which is a common side effect. These can happen during treatment, or after treatment has stopped.
- **Pain or swelling in your legs, especially in your lower leg or calves.**
This may be due to blood clots in the veins of your leg (deep vein thrombosis), which is a common side effect. These can happen during treatment, or after treatment has stopped.

- **Chest pain spreading to the arms, neck, jaw, back or stomach, feeling sweaty and breathless, feeling sick or vomiting.**
These may be symptoms of a heart attack/ myocardial infarction (which may be due to blood clots in the arteries of your heart).
- **Having difficulty in seeing or speaking, which is temporary.**
These may be symptoms of a stroke (which may be due to a clot in an artery in your brain).
- **Fever, chills, sore throat, cough, mouth ulcers or any other symptoms of infection.**
- **Bleeding or bruising in the absence of injury.**

Other side effects include:

It is important to note that a small number of patients with multiple myeloma may develop additional types of cancer, especially haematological malignancies, and it is possible that this risk may be increased with Thalidomide Celgene treatment; therefore your doctor should carefully evaluate the benefit and risk when you are prescribed Thalidomide Celgene.

Very common (may affect more than 1 in 10 people)

- Constipation.
- Feeling dizzy.
- Sleepiness, feeling tired.
- Shaking (tremor).
- Swelling of hands and feet.
- Low blood cell counts. This may mean that you are more likely to develop infections. Your doctor may monitor your blood cell counts during treatment with Thalidomide Celgene.

Common (may affect up to 1 in 10 people)

- Indigestion, feeling sick (nausea), being sick (vomiting), dry mouth.
- Rash, dryness of the skin.
- Feeling weak, faint or unsteady, lack of energy or strength, low blood pressure.
- Fever, feeling generally unwell.
- A spinning feeling in your head, making it difficult to stand up and move normally.
- Blurred vision.
- Chest infection (pneumonia), lung disease.
- A slow heart rate, heart failure.
- Depression, confusion, mood changes, anxiety.

Uncommon (may affect up to 1 in 100 people)

- Inflammation and swelling of the tubes in your lungs (bronchitis).
- Inflammation of the cells lining your stomach wall.
- A hole in part of your large bowel (colon) which can cause infection.

Additional side effects have been reported after this medicine was marketed. These include:

- Underactive thyroid (hypothyroidism).
- Bowel obstruction.
- Sexual dysfunction, for example impotence.
- A fall in the number of white blood cells (neutropenia) accompanied by fever and infection
- Severe blood infection (sepsis) accompanied by fever, chills and severe shaking, and possibly complicated by low blood pressure and confusion (septic shock).
- A fall in the number of red and white blood cells and platelets at the same time (pancytopenia).
- Tumour Lysis Syndrome - metabolic complications that can occur during the treatment of cancer and sometimes even without treatment. These complications are caused by the break-down products of dying cancer cells and may include the following: changes to blood chemistry; high potassium, phosphorus, uric acid, and low calcium consequently leading to changes in kidney function, heart beat, seizures, and sometimes death.

- Allergic reactions such as a localised or generalised pruritic rash and angioedema (types of allergic reaction that may be manifested as hives, rashes, swelling of eyes, mouth or face, difficulty of breathing, or itching).
- Hearing decreased or deafness.
- Convulsions.
- Kidney disease (renal failure).
- Injury to the liver (hepatic disorder) including abnormal liver test results.
- Bleeding from the stomach or bowels (gastrointestinal haemorrhage).
- Irregularities of the heartbeat (heart block or atrial fibrillation), feeling faint or fainting.
- Worsening of Parkinson’s disease symptoms (such as tremor, depression or confusion).
- Pain in the upper abdomen and/or back, which may be severe and which remains for a few days, possibly accompanied by nausea, vomiting, fever and a rapid pulse – these symptoms may be due to the inflammation of the pancreas (pancreatitis).
- Increase in blood pressure within blood vessels that supply the lungs which can lead to shortness of breath, tiredness, dizziness, pain in the chest, a faster heartbeat, or swelling in the legs or ankles (pulmonary hypertension).
- Viral infections, including herpes zoster (also known as ‘shingles’, a viral disease that causes a painful skin rash with blisters) and recurrence of hepatitis B infection (which can cause yellowing of the skin and eyes, dark brown-coloured urine, right-sided stomach pain, fever and feeling nauseous or being sick).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Thalidomide Celgene

Keep out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the wallet card and the blister after EXP. The expiry date refers to the last day of that month.

Do not use if you notice any damage or signs of tampering.

This medicine does not require any special storage conditions.

At the end of your treatment you should return all unused capsules to the pharmacist or doctor. These measures will prevent misuse.

6. Contents of the pack and other information

What Thalidomide Celgene contains

- The active substance is thalidomide. Each capsule contains 50 mg of thalidomide.
- The other excipients are pregelatinized starch and magnesium stearate. The capsule shell contains gelatin and titanium dioxide (E171). The printing ink is composed of shellac, black iron oxide (E172) and propylene glycol.

What Thalidomide Celgene looks like and contents of the pack

Thalidomide Celgene are white hard capsules marked “Thalidomide Celgene 50 mg”. The capsules are supplied in a wallet card containing 28 capsules (2 blisters of 14 capsules each).

Marketing Authorisation Holder and Manufacturer

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

OR

Marketing Authorisation Holder

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

Manufacturer

Penn Pharmaceutical Services Limited
Tafarnaubach Industrial Estate
Tredegar
Gwent
NP22 3AA
United Kingdom

This leaflet was last revised in

Other sources of information

Please contact the Marketing Authorisation Holder if you require this information in another format.

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments.