

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 i-SECURE 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 i-SECURE 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 i-SECURE Pregnancy Prevention Programme are met. The conditions of the i-SECURE 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 ≥ 2 years*.
- Premature ovarian failure confirmed by a specialist gynaecologist.
- Female that has not begun menstruation.
- 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 using two forms of 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 is amenorrheic 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 i-SECURE Pregnancy Prevention Programme
- The patient confirms that he (she) understands the aforementioned conditions.

Contraception

Women of childbearing potential must use two forms of effective methods of contraception for 4 weeks before therapy, during therapy, and during 4 weeks after thalidomide therapy and even in case of dose interruption. 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:

Highly effective methods:

- Intra Uterine Device (IUD)
- Hormonal implants, Levonorgestrel-releasing intrauterine system (IUS)
- Medroxyprogesterone acetate depot injections
- Tubal ligation
- Partner 's vasectomy
- Ovulation inhibitory progesterone-only pills (i.e., desogestrel)

Effective methods:

- Male condom
- Diaphragm
- Cervical cap

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 50 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 7 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 7 days prior to the visit to the prescriber.

Men

As thalidomide is found in semen, male patients must use condoms during treatment and for 4 weeks 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 after the last medically supervised negative pregnancy test result .

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 4 weeks 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/Local Partner will provide educational material to healthcare professionals. The i-SECURE 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 i-SECURE Pregnancy Prevention Programme should be given by the physician to women of childbearing potential and, as appropriate, to male patients.

Amenorrhoea

The use of thalidomide could be associated with menstrual disorders including amenorrhoea. Amenorrhoea 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 amenorrhoea 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 anytime 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 two effective methods 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 4 weeks 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 i-SECURE 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) and 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.

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

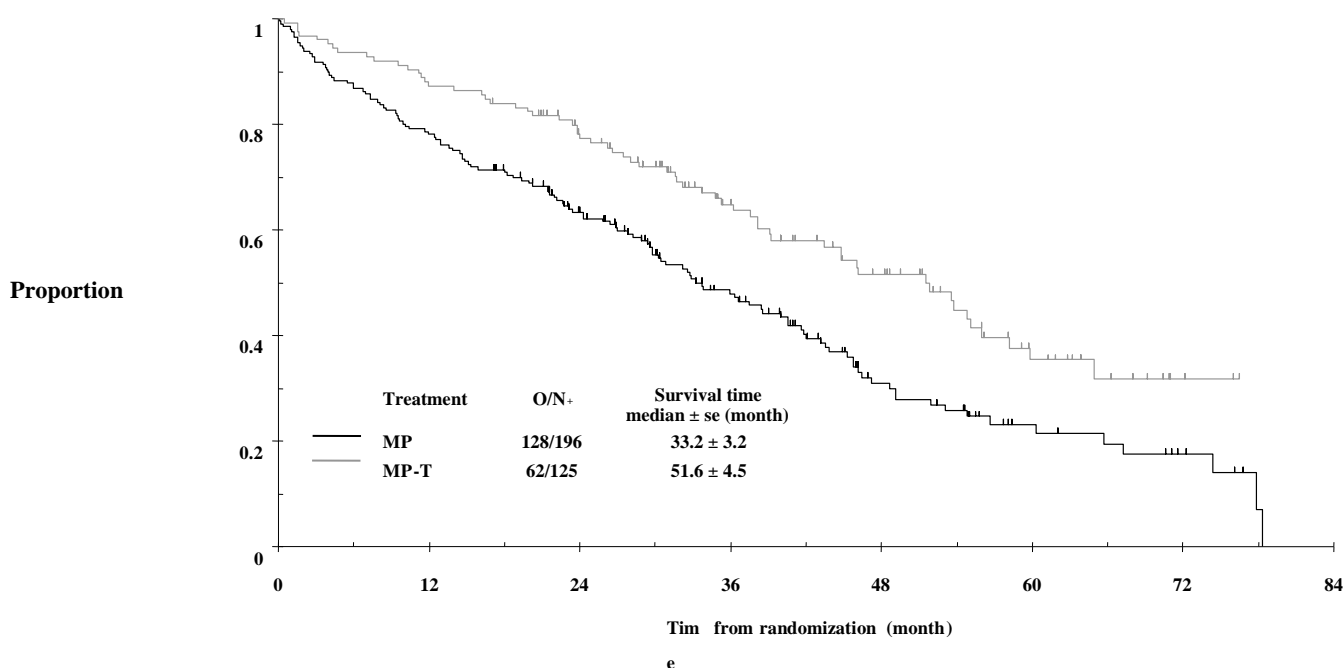
Thalidomide shows immunomodulatory anti-inflammatory and potential anti-neoplastic activities. Data from *in vitro* studies and clinical trials suggest that the immunomodulatory, anti-inflammatory and anti-neoplastic effects of thalidomide may be related to suppression of excessive tumour necrosis factor-alpha (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 47-133kg, thalidomide clearance ranged from approximately 6-12 L/h, representing an increase in thalidomide clearance of 0.621 L/h per 10kg 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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store below 30°C

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

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