



Thalidomide Celgene™ ▼

Summary of Product Characteristics

UK







50 mg hard capsules (thalidomide)

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.

Excipient:

Each capsule contains 257.2 mg of anhydrous lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule.

White opaque capsules marked "Thalidomide 50 mg Celgene".

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).

Recommended posology in adults:

The recommended oral dose is 200 mg per day.

A maximum number of 12 cycles of 6 weeks should be used.

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

Patients should be monitored for: thromboembolic events; peripheral neuropathy; rash/skin reactions; bradycardia, syncope and somnolence (see sections 4.4 and 4.8). Dose delay, reduction or discontinuation, dependent upon the NCI CTC 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.

Peripheral neuropathy:

Dose modifications due to peripheral neuropathy are described in Table 1.

Table 1: 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 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:

No specific dose adjustments are recommended for the elderly.

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 patients:

Thalidomide Celgene is not recommended for use in children below 18 years of age as safety and efficacy have not been established.

4.3 Contraindications

- Hypersensitivity to thalidomide or to any of the excipients.
- 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 \geq 50 years and naturally amenorrhoeic for \geq 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 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.
- 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 the patient 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.

Deep venous thrombosis and pulmonary embolism:

An increased risk of deep venous thrombosis (DVT) and pulmonary embolus (PE) has been reported in patients treated with thalidomide (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 thrombotic risk in these patients. Therefore, these agents should be used with caution in multiple myeloma patients receiving thalidomide with prednisone and melphalan. Particularly, a haemoglobin concentration above 12g/dl should lead to discontinuation of erythropoietic agents.

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

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 and bradycardia:

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

Skin reactions:

If at anytime the patient experiences a toxic skin reaction e.g. Stevens-Johnson 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.

Patients with renal or hepatic impairment:

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

Lactose intolerance:

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

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 metabolized by this enzyme system are unlikely.

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 Pregnancy and lactation

Thalidomide Celgene 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.

Women of childbearing potential:

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.

Male patients with female partners of childbearing potential:

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 with childbearing potential who is not using effective contraception.

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

Lactation:

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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

However thalidomide may cause 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

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

The clinically important adverse reactions 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).

Table 2 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 related to thalidomide in combination with dexamethasone and also those based on post-marketing experience with the medicinal product are provided after Table 2.

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 ($< 1/10,000$, not known (cannot be estimated from the available data)). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Frequency of adverse reactions with thalidomide in combination with melphalan and prednisone

System Organ Class	Very Common	Common
Cardiac disorders		Cardiac failure Bradycardia
Blood and lymphatic system disorders	Neutropenia Leukopenia Anaemia Lymphopenia Thrombocytopenia	
Nervous system disorders	Peripheral neuropathy* Tremor Dizziness Paraesthesia Dysaesthesia Somnolence	Abnormal coordination
Respiratory, thoracic and mediastinal disorders		Pulmonary embolism* Interstitial lung disease Bronchopneumopathy Dyspnea
Gastrointestinal disorders	Constipation	Vomiting Dry mouth
Skin and subcutaneous tissue disorders		Toxic skin eruption Rash Dry skin
Infections and infestations		Pneumonia
Vascular disorders		Deep vein thrombosis*
General disorders and administration site conditions	Peripheral oedema	Pyrexia Asthenia Malaise
Psychiatric disorders		Confusional state Depression

* - See detailed section opposite

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.

Additional adverse reactions related to post-marketing experience with thalidomide and not seen in the pivotal study include: toxic epidermal necrolysis, intestinal obstruction, hypothyroidism, sexual dysfunction, tumour lysis syndrome and gastro-intestinal perforations.

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 3)

Table 3: 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 reaction from post-marketing experience with thalidomide and not seen in the pivotal study include febrile neutropenia.

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).

Thromboembolic events:

An increased risk of DVT and PE 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.

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: immunosuppressive agent, ATC code: LO4AX 02.

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.

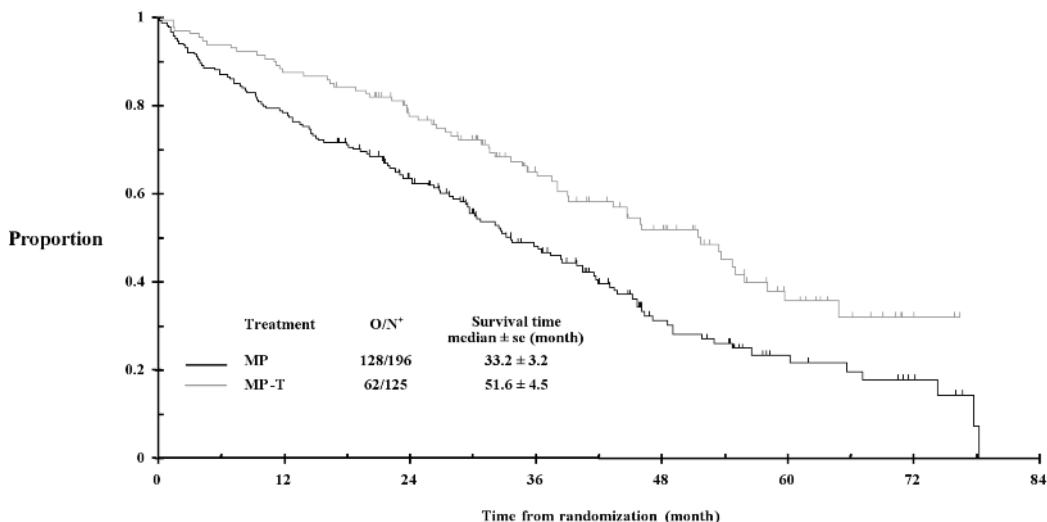
Thalidomide shows immunomodulatory anti-inflammatory and potential anti-neoplastic activities. Data from *in vitro* studies and clinical trials suggest that the immunomodulatory, anti-inflammatory and anti-neoplastic effects of thalidomide may be related to suppression of excessive tumour necrosis factor- α (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:

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



5.2 Pharmacokinetic properties

Absorption:

Absorption of thalidomide is slow after oral administration. The maximum plasma concentrations are reached 2-5 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).

Metabolism:

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. Total systemic exposure (AUC) is proportional to dose at single-dose conditions. No time dependency of the pharmacokinetics has been observed. Following a single oral dose of 400mg 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.

Hepatic and renal insufficiency:

The pharmacokinetics of thalidomide in patients with impaired renal or hepatic function is unknown. Considering that pharmacologically active metabolites are eliminated via urine, patients with severe renal impairment should be carefully monitored for 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:

Anhydrous lactose
Microcrystalline cellulose
Crospovidone (Type A)
Povidone (K90)
Stearic acid
Colloidal anhydrous silica

Capsule shell:

Gelatin
Titanium dioxide (E171)

Printing ink:

Shellac
Black iron oxide (E172)
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 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/PE/Aclar/aluminium blister containing 14 capsules
Pack sizes: 28 capsules (two blisters) in a wallet card.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd, Riverside House, Riverside Walk, Windsor SL4 1NA, United Kingdom
Tel: +44 (0)1753 240600 Fax: +44 (0)1753 240899

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/443/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/04/2008

10. DATE OF REVISION OF THE TEXT

23/03/2010

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

