PRODUCT MONOGRAPH

Pr THALOMID®

Thalidomide Capsules House Standard

50 mg, 100 mg, 200 mg

Immunomodulatory Agent

Celgene Inc.*
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Suite 300
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* a Bristol Myers Squibb company

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Oral	Capsule, 50 mg, 100 mg, 200 mg	Capsule shells contain gelatin *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

THALOMID® (thalidomide capsules) in combination with melphalan and prednisone (MPT) is indicated for the treatment of patients with previously untreated multiple myeloma who are 65 years of age or older.

Distribution restrictions
THALOMID® is only available through a controlled distribution program called RevAid®. Under this program, only prescribers and pharmacists registered with the program are able to prescribe and dispense the product. In addition, THALOMID® can only be dispensed to patients who are registered and meet all the conditions of the RevAid® program. Please call 1-888-RevAid1 (1-888-738-2431) or log onto www.revaid.ca.

Geriatrics: THALOMID® has been used in clinical trials in patients up to 92 years of age. For patients > 75 years of age, the recommended starting dose of THALOMID® is 100 mg/day (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics and DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).

Pediatrics (< 19 years of age):
The safety and effectiveness of THALOMID® in children and adolescents < 19 years of age have not been established. THALOMID® is not recommended for use in children under 19 years of age.

CONTRAINDICATIONS

- Due to its known human teratogenicity, even following a single dose, THALOMID® (thalidomide capsules) is contraindicated in females who are pregnant and females at risk of becoming pregnant (see **WARNINGS and PRECAUTIONS**).

- THALOMID® is contraindicated in patients who have known hypersensitivity to thalidomide or to lenalidomide, pomalidomide or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

- Breast feeding women.

- Male patients unable to follow or comply with the required contraceptive measures (see **WARNING AND PRECAUTIONS, Special Populations – Male Patients).**

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

THALOMID® (thalidomide capsules) should be initiated and monitored under the supervision of a physician qualified in the use of cancer therapies and a full understanding of the risks of thalidomide therapy and monitoring requirements.

- Causes human birth defects, stillbirths and spontaneous abortions (see **WARNINGS AND PRECAUTIONS, Special Populations - Females of Child-Bearing Potential** and **Male patients**)

- Peripheral Neuropathy (see **WARNINGS AND PRECAUTIONS, Neurologic**)

- Thromboembolic events, venous and arterial (see **WARNINGS AND PRECAUTIONS, Cardiovascular, Special Populations - Females of Child-Bearing Potential, ADVERSE REACTIONS and DRUG INTERACTIONS**)

- Hepatotoxicity, including fatal cases (see **WARNINGS AND PRECAUTIONS**, **Hepatic**)

- Anaphylaxis (see **WARNINGS AND PRECAUTIONS**, **Hypersensitivity**)

- Available only under a controlled distribution program called RevAid®.

General

Thalidomide is a powerful human teratogen, inducing a high frequency of severe and life-threatening birth defects. Thalidomide must never be used by females who are pregnant. Thalidomide must never be used by Females of Child-Bearing Potential unless all aspects of the

controlled distribution program RevAid® are fulfilled. The conditions of the RevAid® program must be fulfilled for all male and female patients.

The only type of thalidomide exposure known to result in drug associated birth defects is as a result of direct oral ingestion of thalidomide. Currently no specific data are available regarding the cutaneous absorption or inhalation of thalidomide in Females of Child-Bearing Potential and whether these exposures may result in any birth defects. Patients should be instructed to not extensively handle or open the capsules and to maintain storage of capsules in blister packs until ingestion wherever possible. If there is contact with non-intact THALOMID® capsules or the powder contents, the exposed area should be washed with soap and water.

Thalidomide has been shown to be present in the serum and semen of patients receiving THALOMID®. If healthcare providers or other care givers are exposed to body fluids from patients receiving THALOMID®, appropriate precautions should be utilized, such as wearing gloves to prevent the potential cutaneous exposure to THALOMID® or the exposed area should be washed with soap and water.

Patients should be informed to not give blood while taking THALOMID® and for 4 weeks after stopping THALOMID®. If a woman who is pregnant received their donated blood, her baby may be exposed to thalidomide and may be born with birth defects.

Carcinogenesis and Mutagenesis

Two-year carcinogenicity studies were conducted in male and female rats and mice. No compound-related carcinogenic effects were observed (see **TOXICOLOGY**).

Thalidomide was neither mutagenic nor clastogenic in the following assays: the Ames bacterial (S. typhimurium and E. coli) reverse mutation assay, a Chinese hamster ovary cell (AS52/XPRT) forward mutation assay, and an in vivo mouse micronucleus test (see **TOXICOLOGY**).

Cardiovascular

Dizziness and Orthostatic Hypotension: Patients should be advised that THALOMID® may cause dizziness and orthostatic hypotension and that, therefore, they should sit upright for a few minutes prior to standing up from a recumbent position.

Bradycardia/Syncope/Atrioventricular Block/Cardiac Failure: Bradycardia in association with thalidomide use has been reported. Some of the reported cases of bradycardia required medical interventions. The clinical significance and underlying etiology of the bradycardia noted in some thalidomide-treated patients are presently unknown. Patients should be monitored for syncope, bradycardia and atrioventricular block; dose reduction or discontinuation may be required.

Thromboembolic Events: The use of THALOMID® in multiple myeloma (MM) results in an increased risk of venous thromboembolic events (VTE), such as deep vein thrombosis (DVT) and pulmonary embolism (PE), and arterial thromboembolic events, such as myocardial infarction and cerebrovascular events. The risk appears to be greatest during the first 5 months of therapy. This risk increases significantly when THALOMID® is used in combination with standard chemotherapeutic agents and/or steroids.

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 MM patients receiving THALOMID® with prednisone and melphalan. The use of hormonal contraceptives is associated with an increased risk of thromboembolic disorders. Hormonal contraceptives are not recommended (see **Special Populations, Females of Child-Bearing Potential**).

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, or arm or leg swelling. Prophylactic antithrombotic medicinal products, such as low molecular weight heparins (LMWH) or warfarin, should be recommended. Thromboprophylaxis should be recommended especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors (see **DOSAGE AND ADMINISTRATION, Recommended dose and Dosage Adjustment**).

Myocardial Infarction: Myocardial infarction has been reported in patients receiving THALOMID®, particularly those with known risk factors. Consequently, patients with known risk factors should be closely monitored and action should be taken to minimize risk factors (e.g. smoking, hypertension, and hyperlipidemia) (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

Dependence

Physical and psychological dependence have not been reported in patients taking THALOMID®.

Hematologic

Neutropenia or Thrombocytopenia: Decreased blood cell counts, including neutropenia or thrombocytopenia, including Grade 3 or 4 occurrences for both events, have been reported in association with the clinical use of THALOMID® in combination with melphalan and prednisone. Patients should be monitored and dose reduction, delay, or discontinuation may be required (see **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests** and **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**). Patients and physicians are advised to be observant for signs and symptoms of bleeding including petechiae, epistaxis, and renal, conjunctival, and gastrointestinal bleeding, especially in case of concomitant medication susceptible to induce bleeding (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

Hepatic

Hepatic disorders, mainly abnormal liver test results, were reported. Serious and fatal cases of liver injury 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 THALOMID® discontinuation. Patients should be monitored for liver function periodically, specifically but not limited to cases with pre-existing liver disorder or concomitant use of medication susceptible to induce liver dysfunction.

Immune

Increased HIV Viral Load: In a randomized, placebo controlled trial of THALOMID® in an HIV-seropositive patient population, plasma HIV RNA levels were found to increase (median change = 0.42 $\log_{10}$ copies HIV RNA/mL, p = 0.04 compared to placebo). A similar trend was observed in a second, unpublished study conducted in patients who were HIV- seropositive. The clinical significance of this increase is unknown. Both studies were conducted prior to availability of highly active antiretroviral therapy. Until the clinical significance of this finding is further understood, in HIV-seropositive patients, viral load should be measured after the first and third months of treatment and every 3 months thereafter.

Infections

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

Hepatitis B Virus Reactivation: Reactivation of hepatitis B virus (HBV) has been reported in THALOMID®-treated patients who have previously been infected with HBV. Some of these cases progressed to acute hepatic failure or fulminant hepatitis, and resulted in permanent discontinuation of THALOMID® or were fatal.

Caution should be exercised when THALOMID® is used in patients previously infected with HBV. These patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. See **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**.

Progressive Multifocal Leukoencephalopathy: Cases of progressive multifocal leukoencephalopathy (PML), including fatal outcomes, have been reported with THALOMID®. Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioural signs or symptoms. Appropriate diagnostic measures for PML are recommended. If PML is suspected, further THALOMID® dosing must be suspended until PML has been excluded. If PML is confirmed, THALOMID® must be permanently discontinued.

Neurologic

Peripheral Neuropathy: THALOMID® is known to cause nerve damage. Peripheral neuropathy (sensory and /or motor) is a very common, potentially severe adverse reaction to treatment with THALOMID® that may be irreversible. Peripheral neuropathy generally occurs following chronic use over a period of months; however, reports following relatively short-term use also exist. The correlation with cumulative dose is unclear. Symptoms may occur some time after THALOMID® treatment has been stopped and may resolve slowly or not at all. THALOMID® may also potentially aggravate existing neuropathy and should not be used in patients with clinical signs or symptoms of peripheral neuropathy.

It is recommended that clinical and neurological examinations are performed in patients prior to starting THALOMID®. Patients should be examined at monthly intervals for the first 3 months

of therapy to enable the clinician to detect early signs of neuropathy, which include numbness, tingling or pain in the hands and feet. Patients should be evaluated periodically thereafter during treatment. Closer monitoring should be carried out during treatment with any concomitant therapy associated with peripheral neuropathy. Patients should be regularly counseled, questioned, and evaluated for signs or symptoms of peripheral neuropathy (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).
Medications known to be associated with neuropathy should be used with caution in patients receiving THALOMID®.

Drowsiness and Somnolence: THALOMID® frequently causes drowsiness and somnolence. Patients should be instructed to avoid situations where drowsiness may be a problem and not to take other medications that may cause drowsiness without adequate medical advice. Such medications include anxiolytics, hypnotics, antipsychotics, H1 anti-histamines, opiate derivatives, barbiturates and alcohol. Patients should be advised as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks, such as driving a car or operating other complex or dangerous machinery. Patients should be instructed that THALOMID® may potentiate the somnolence caused by alcohol. Patients should be monitored and dose reduction may be required (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).

Seizures: Seizures, including grand mal convulsions, have been reported during post-marketing experience with THALOMID®. Most patients had disorders that may have predisposed them to seizure activity, and it is not currently known whether THALOMID® has any epileptogenic influence. During therapy with THALOMID®, patients with a history of seizures or with other risk factors for the development of seizures should be monitored closely for clinical changes that could precipitate acute seizure activity.

Hypersensitivity
Hypersensitivity reactions to THALOMID® including anaphylaxis has been reported. Signs and symptoms have included the occurrence of erythematous macular rash, possibly associated with fever, tachycardia, and hypotension, and if severe, may necessitate interruption of therapy. If the reaction recurs when dosing is resumed, THALOMID® should be discontinued. If anaphylactic reaction or angioedema occurs, use of THALOMID® should not be resumed.

Skin

Serious dermatologic reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which may be fatal, have been reported. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. THALOMID® should be interrupted or discontinued if a Grade 2-3 skin rash occurs and only resumed following appropriate clinical evaluation. If the rash is Grade 4, exfoliative, purpuric, or bullous or if SJS, TEN or DRESS is suspected, use of THALOMID® should not be resumed. Caution should be exercised when THALOMID® is given with drugs known to cause serious skin reactions.

Tumor Lysis Syndrome
Patients at risk for Tumor Lysis Syndrome are those with high tumor burden prior to treatment. These patients should be monitored closely, and appropriate precautions taken.

Second Primary Malignancies - Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS)
A statistically significant increase of AML and MDS was observed in one clinical trial in patients with previously untreated MM receiving the combination melphalan, prednisone, and THALOMID® (MPT). In patients receiving MPT, the hematologic SPM incidence rate (0.72 per 100 person-years) was increased as compared to lenalidomide in combination with dexamethasone (0.17 per 100-patient years). AML and MDS have been reported in the post-market setting (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**). The risk of AML and MDS must be taken into account before initiating treatment with THALOMID® in combination with melphalan and prednisone (MPT). Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as indicated.

Special Populations

1. Females of Child-Bearing Potential:

Females of Child-Bearing Potential are all females who are menstruating, amenorrheic from previous treatments, and/or perimenopausal.

The most serious toxicity associated with thalidomide is its documented human teratogenicity. The risk of severe birth defects, primarily phocomelia or death to the fetus, is extremely high. The critical period of pregnancy is estimated, depending on the source of information, to range from 35 to 50 days after the last menstrual period. The risk of other potentially severe birth defects outside this critical period is unknown, but may be significant. Based on present knowledge, THALOMID® must not be used at any time during pregnancy. Even if a single dose [1 capsule (50 mg, 100 mg or 200 mg)] of THALOMID® is taken during pregnancy, it can cause severe birth defects or death to an unborn baby.

For Females of Child-Bearing Potential, THALOMID® is contraindicated unless **ALL** of the following conditions are met:

- ✓ The patient is capable of understanding and carrying out instructions. (In some cases, the patient will need a competent support person to ensure RevAid® program compliance).

- ✓ The patient is willing and able to comply with the **two** mandatory, simultaneous and effective contraceptive measures or to commit to continually abstaining from heterosexual contact.

- ✓ The patient has a consultation with a health care professional, who has experience with the use of contraceptive methods, to discuss the best and most effective **two** simultaneous contraceptive methods to be used.

- ✓ The patient understands the cumulative risks of deep venous thrombosis, including, but not limited to, THALOMID®, cancer and hormonal contraception.

- ✓ The patient knows the risk of possible contraceptive failure.

- ✓ The patient is willing and able to comply with the pregnancy testing requirements noted in detail below. This includes two negative pregnancy tests prior to the first dispense and on-going pregnancy tests throughout treatment.

- ✓ The patient is aware of the potential need for emergency contraception.

- ✓ The patient is informed of the risk of teratogenicity should a pregnancy occur.

- ✓ The patient knows and understands the need to consult her physician immediately if there is a risk of pregnancy.

- ✓ The patient acknowledges the importance of compliance with all the conditions of use.

Contraceptive Measures:

- All Females of Child-Bearing Potential (including those who normally do not use contraception due to a history of infertility, and those who have amenorrhea) must use the two simultaneous, effective methods of contraception:
    - For at least 4 weeks before starting THALOMID® treatment.
    - During dose interruptions.
    - During THALOMID® treatment.
    - For at least 4 weeks following the discontinuation of THALOMID® treatment.
- The patient who chooses to abstain from heterosexual contact as a contraceptive measure, must commit to using 2 methods of contraception at the same time if abstinence is no longer practiced.

- The use of hormonal contraceptives is associated with an increased risk of thromboembolic disorders. Hormonal contraceptives are not recommended (see **WARNINGS AND PRECAUTIONS, Hematologic**).

- Any method of contraception can fail. It is, therefore, critically important that Females of Child-Bearing Potential use two effective methods of contraception simultaneously.

- If pregnancy does occur during treatment, the drug should be immediately discontinued. Under these conditions, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity, for further evaluation and counseling.

- Any suspected embryo-fetal exposure to THALOMID® should be reported to Celgene at 1-888-RevAid1 (1-888-738-2431)

- Female patients with a previous hysterectomy or bilateral oophorectomy are exempt from contraception use during THALOMID® therapy.

Pregnancy Testing:

- Females of Child-Bearing Potential must not be given THALOMID® until pregnancy is excluded. The patient must have two negative pregnancy tests before starting THALOMID® therapy, as well as subsequent tests throughout the treatment.

- The first pregnancy test should be conducted seven to 14 days prior to the start of therapy.

- The second pregnancy test should be conducted 24 hours prior to dispensing and starting the drug.
- A pregnancy test should be conducted weekly during the first month of treatment, monthly thereafter during treatment (or every two weeks if menses are irregular) and 4 weeks after the discontinuation of treatment.

- The pregnancy test should be a blood test performed in a licensed laboratory. The dates and results of pregnancy tests should be documented.

- The pregnancy test should have a serum hCG sensitivity of at least 25 mIU/ml.

- Pregnancy testing and consultation with an obstetrician/gynecologist should also occur if a patient misses her period, or if there is any abnormal menstrual bleeding.

2. Pregnant Women:

- THALOMID® is contraindicated in females who are, or may become, pregnant.

- THALOMID® is contraindicated in Females of Child-Bearing Potential who are not using the two mandatory, simultaneous and effective methods of contraception or who are not continually abstaining from heterosexual sexual contact.

- Even if a single dose [1 capsule (50 mg, 100 mg or 200 mg)] of THALOMID® is taken during pregnancy, it can cause severe birth defects or death to an unborn baby.

- If pregnancy does occur during treatment, the drug should be immediately discontinued. Under these conditions, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity, for further evaluation and counseling.
- Any suspected embryo-fetal exposure to THALOMID® should be reported to Celgene at 1-888-RevAid1 (1-888-738-2431).

3. Nursing Women:

- THALOMID® should not be used when a patient is breast-feeding.

4. Male Patients:

Thalidomide is present in the semen of males who take THALOMID®. (See **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**, **Distribution**). There is a potential risk of birth defects, stillbirths and spontaneous abortions if a developing fetus is exposed to thalidomide through the semen of male patients (see **WARNINGS AND PRECAUTIONS**, **Females of Child-Bearing Potential**). Therefore, males receiving THALOMID® must always use a condom during any sexual contact with Females of Child-Bearing Potential even if they have undergone a successful vasectomy. The condom should be used:

- While the Male Patient is taking THALOMID®.
- During interruption of treatment.
- For at least 4 weeks after stopping THALOMID®.

Patients should not donate semen while taking THALOMID®, and for at least 4 weeks after stopping THALOMID®.

Male patients must inform their female sexual partners of child-bearing potential that:

- The male patient is taking THALOMID®.
- There is a potential risk of birth defects, stillbirths and spontaneous abortions if a developing fetus is exposed to the semen of the male patient.
- A condom must be used during any sexual contact.

If a pregnancy occurs in a partner of a male patient taking thalidomide, it is recommended to refer the female partner to a physician specialized or experienced in teratology for evaluation and advice.

5. Pediatrics (< 19 years of age):

Safety and effectiveness in pediatric patients below the age of 19 years of age have not been established. THALOMID® is not recommended for use in children under 19 years of age. For

ALL sexually active Females of Child-Bearing Potential the use of two simultaneous, effective methods of contraception is mandatory (see **WARNINGS AND PRECAUTIONS, Special Populations – Females of Child-Bearing Potential**).

6. Geriatrics:

THALOMID® has been used in clinical trials in patients up to 92 years of age. For patients > 75 years of age, the recommended starting dose of THALOMID® is 100 mg/day (see **INDICATIONS AND CLINICAL USE, Geriatrics and DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).

The adverse reaction profile reported in patients > 75 years of age treated with THALOMID® 100 mg daily was similar to the adverse reaction profile observed in patients ≤ 75 years of age treated with THALOMID® 200 mg once daily. However, the overall frequency of serious (such as atrial fibrillation, back pain, and fall) including fatal adverse reactions was higher in patients > 75 years of age treated with THALOMID® 100 mg daily, possibly due to additional co-morbidities and risk factors (see **ADVERSE REACTIONS, Adverse Drug Reactions from Other Clinical Trials**).

Monitoring and Laboratory Tests

Complete Blood Count (CBC) and serum chemistries should be evaluated approximately monthly. White blood cell count and differential, and platelets should be monitored on an ongoing basis, in accordance with oncology guidelines especially in patients who may be more prone to neutropenia and thrombocytopenia, respectively.

Patients should be monitored for liver function periodically, specifically but not limited to cases with pre-existing liver disorder or concomitant use of medication susceptible to induce liver dysfunction.

In an HIV-seropositive patient population, plasma HIV RNA levels were found to increase. Until the clinical significance of this finding is further understood, in HIV-seropositive patients, viral load should be measured after the first and third months of treatment and every 3 months thereafter.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

THALOMID® (thalidomide capsules) is a powerful human teratogen, inducing a high frequency of severe and life-threatening birth defects.

In general, in controlled studies in patients treated for MM, the overall incidence of adverse reactions in the THALOMID® treatment group was higher than in patients treated in the comparator arms. This was also true for serious adverse reactions, discontinuations due to adverse reactions, and adverse reactions that led to discontinuation of study drug or dose reduction or interruption. However, the percentages of patients who died due to adverse drug reactions were similar between treatment groups.

Most patients taking THALOMID® in combination with melphalan and prednisone (MPT) can be expected to experience adverse reactions.

The most frequently reported (≥ 10%) adverse reactions in THALOMID® treated patients (when taken as MPT) in clinical trials were constipation, nausea, rash, somnolence/fatigue, dizziness, peripheral sensory neuropathy, paraesthesia, tremor, peripheral edema, asthenia, and hematological adverse events (neutropenia, anemia, thrombocytopenia, leucopenia, lymphopenia). Events of deep vein thrombosis and pulmonary embolism (DVT/PE) were also reported, generally at higher rates in the THALOMID® treatment groups.

Clinical Trial Adverse Drug Reactions

Treatment of Multiple Myeloma in Subjects Aged 65 to 75 Years (Study IFM 99-06)

IFM-99-06 was a multicentre, randomized, open-label study comparing MPT versus MP in patients ≥ 65 years of age with previously untreated MM. Patients less than 65 years of age were included if they were ineligible for high-dose therapy.

Patients were excluded from participation in the trial if they had serum creatinine ≥ 50 mg/L, impaired cardiac function, signs of cerebral circulatory insufficiency, peripheral neuropathy or significant impairment of hepatic function.

Patients were to receive up to 12 cycles of treatment, with each cycle lasting 6 weeks (total of 72 weeks). All patients received at least 1 week of study drug. The median duration of treatment in the MPT group was 10.5 months and ranged up to 26.9 months. The median dose of THALOMID® in the MPT group was 217.4 mg and ranged up to 400 mg.

At study start, equal proportions of patients received an initial daily dose of thalidomide of 200 mg and 400 mg (44.4% of patients for each dose). The majority of patients remained stable on the 200 mg dose of THALOMID® during the first 12 months of the study, after which an increasing proportion of patients either had their dose reduced or discontinued thalidomide.

According to the IFM sponsored protocol, events that were considered by the investigator to be of Grades 1 and 2 were not collected on the case report form unless they were identified as events of interest based on the known adverse effects of thalidomide (e.g. skin, cardiac, thrombotic or neurological toxicity events). Events of interest were reported for all grades. In addition, all of those AEs that were life-threatening or death events were reported as serious and were therefore included in the safety assessment of the use of melphalan, prednisone and thalidomide.

The most commonly observed adverse reactions associated with the use of THALOMID® in combination with melphalan and prednisone are: neutropenia, leukopenia, constipation, somnolence, paresthesia, peripheral neuropathy, anemia, lymphopenia, thrombocytopenia, dizziness, dysesthesia, tremor and peripheral edema (Table 1).

The clinically important adverse reactions associated with the use of THALOMID® in combination with melphalan and prednisone include: DVT, PE, peripheral neuropathy, severe

skin reactions including Stevens Johnson Syndrome and toxic epidermal necrolysis, syncope, bradycardia and dizziness.

Table 1: Most Commonly Reported Adverse Reactions in ≥ 10% of subjects treated in the THALOMID®, Melphalan and Prednisone arm in the Previously Untreated Multiple Myeloma Study IFM 99-06 of MPT vs MP

Organ System Class/Preferred Term	MPT (N=124)		MP (N=193)	
	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)
Blood and Lymphatic System Disorders				
Neutropenia	55 (44)	58 (47)	59 (31)	63 (33)
Leukopenia	35 (28)	35 (28)	32 (17)	32 (17)
Anemia	26 (21)	27 (22)	37 (19)	38 (20)
Lymphopenia	19 (15)	19 (15)	14 (7)	14 (7)
Thrombocytopenia	14 (11)	15 (12)	22 (11)	23 (12)
Nervous System Disorders				
Somnolence	2 (2)	28 (23)	0	0
Paresthesia	3 (2)	23 (19)	0	4 (2)
Peripheral Neuropathy	2 (2)	21 (17)	0	0
Dizziness	1 (1)	15 (12)	0	5 (3)
Dysesthesia	1 (1)	15 (12)	0	1 (0.5)
Neuropathy	1 (1)	15 (12)	0	0
Tremor	0	14 (11)	0	0
General Disorders and Administrative Site Conditions				
Peripheral edema	0	15 (12)	0	3 (2)
Gastrointestinal Disorders				
Constipation	0	28 (23)	0	1 (0.5)

In Study IFM 99-06, skin, neurological, cardiac, and thrombotic events of all WHO grades or intensities were reported. For all other AEs, only those of WHO Grades 3 or of severe intensity were reported and only if, according to the investigator, they were not attributable to progression of the myeloma.

Less Common Clinical Trial Adverse Drug Reactions (< 10%)

Blood and Lymphatic System Disorders: febrile bone marrow aplasia, febrile neutropenia, pancytopenia

Cardiac Disorders: cardiac failure, bradyarrhythmia, sinus bradycardia

Gastrointestinal Disorders: vomiting, dry mouth, nausea, diarrhea, abdominal pain upper

General Disorders and Administration Site Conditions: asthenia, pyrexia, malaise, general physical health deterioration, edema, fatigue

Infections and infestations: herpes zoster, pneumonia, oral fungal infection

Metabolism and Nutrition Disorders: hyperkalemia, hypokalemia

Musculoskeletal, Connective Tissue, and Bone Disorders: back pain

Nervous System Disorders: peripheral sensory neuropathy, coordination abnormal, balance disorder, coma, gait disturbance, hypoesthesia, cognitive disorder, polyneuropathy

Psychiatric Disorders: depression, confusional state

Renal and Urinary Disorders: renal failure acute

Reproductive System and Breast Disorders: sexual dysfunction

Respiratory, Thoracic and Mediastinal Disorders: dyspnea, pulmonary embolism, acute pulmonary edema, bronchopneumopathy, interstitial lung disease

Skin and subcutaneous tissue disorders: toxic skin eruption, dry skin, rash

Vascular Disorders: deep vein thrombosis, hypotension, phlebitis, thrombosis, venous thrombosis, venous thrombosis limb, thrombophlebitis

Adverse Drug Reactions from Other Clinical Trials

In an additional study, in patients with previously untreated MM, in which THALOMID® (as MPT) was a comparator arm, the most frequently reported adverse events (≥ 20%) were: neutropenia, constipation, anemia, peripheral edema, peripheral sensory neuropathy, nausea, fatigue, and thrombocytopenia. The proportion of patients with at least one grade 3 or 4 adverse event was 89%. The most frequently reported Grade 3 or 4 adverse events were: blood disorders namely, neutropenia, anemia, thrombocytopenia, leucopenia, and lymphopenia; and peripheral sensory neuropathy.

Patients' age ranged from 51-92. Subgroup analyses were performed by age (≤ 75 and > 75 years of age). The adverse reaction profile reported in patients > 75 years of age treated with THALOMID® 100 mg daily was similar to the adverse reaction profile observed in patients ≤ 75 years of age treated with THALOMID® 200 mg once daily.

The most frequently reported adverse events (≥ 20%) in patients > 75 years of age were: neutropenia, constipation, anemia, peripheral edema, peripheral sensory neuropathy, fatigue, nausea, asthenia, back pain, and thrombocytopenia. The most frequently reported serious adverse events (≥ 2%) in patients > 75 years of age were: pneumonia, anemia, atrial fibrillation, back pain, febrile neutropenia, general physical health deterioration, cardiac failure, pulmonary embolism, acute renal failure, dyspnea, fall, neutropenia, renal failure, sepsis and syncope. The serious adverse events of atrial fibrillation, back pain and fall were more frequently (with a difference of ≥ 2%) reported in patients > than 75 years of age than younger patients, possibly due to additional co-morbidities and risk factors.

In two studies of THALOMID® in combination with dexamethasone in the treatment of previously untreated MM, the following adverse reactions were observed in ≥ 10% of patients: peripheral neuropathy, tremor, dizziness, confusion, DVT/PE, constipation, peripheral edema, fatigue, dry skin, anemia, vision blurred, dry mouth, asthenia, WBC count decreased, depressed level of consciousness, paresthesia, anxiety and hypotension.

Post-Market Adverse Drug Reactions

Somnolence, dizziness, neuropathy and rash are the most commonly observed adverse events associated with the use of THALOMID®. THALOMID® has been studied in controlled and uncontrolled clinical trials in patients with MM and Erythema Nodosum Leprosum (ENL) and in people who are HIV-seropositive. In addition, thalidomide has been administered investigationally for more than 20 years in numerous indications.

Table 2 provides the adverse drug reactions from post-marketing experience for patients that have been exposed to THALOMID® since February 1997.

Table 2: Adverse Reactions reported from February 1997 to February 2013			
Body System	**Common (≥ 1% and < 10%)**	**Uncommon (≥ 0.1% and < 1%)**	**Rare (≥ 0.01% and < 0.1%)**
Blood and lymphatic system disorders		Anemia, Leucopenia, Neutropenia, Thrombocytopenia	Bone marrow failure, Febrile neutropenia, Lymphopenia, Pancytopenia
Cardiac disorders		Bradycardia	Arrhythmia, Atrial fibrillation, Cardiac arrest, Cardiac disorder, Cardiac failure, Cardiac failure congestive, Cardio-respiratory arrest, Myocardial infarction, Palpitations, Sinus bradycardia, Tachycardia, Atrioventricular block
Ear and labyrinth disorders			Deafness, Tinnitus, Vertigo
Endocrine disorders			Hypothyroidism
Eye disorders			Diplopia, Vision blurred, Visual disturbance
Gastrointestinal disorders		Constipation, Diarrhea, Nausea, Vomiting	Abdominal distension, Abdominal pain, Abdominal pain upper, Ascites, Colitis, Dry mouth, Dyspepsia, Dysphagia, Gastrointestinal disorder, Gastrointestinal hemorrhage (including fatalities), Hypoesthesia oral, Intestinal obstruction, Intestinal perforation, Pancreatitis, Paresthesia oral, Stomach discomfort, Stomatitis
General disorders and administration site conditions	Death, Disease progression	Asthenia, Condition aggravated, Drug ineffective, Drug intolerance, Fatigue, Malaise, Edema peripheral, Pain, Pyrexia	Chest pain, Chills, Drug interaction, Face edema, Feeling abnormal, Gait disturbance, General physical health deterioration, Hyperpyrexia, Influenza like illness, Mucosal inflammation, Multi-organ failure, Edema, Sudden death, Swelling,
Hepatobiliary disorders			Hepatic failure, Jaundice
Immune system disorders			Graft versus host disease, Hypersensitivity
Infections and infestations[a]		Pneumonia, Sepsis	Bronchitis, Cellulitis, Herpes zoster, Infection, Septic shock, Sinusitis, Staphylococcal infection, Upper respiratory tract infection, Urinary tract infection
Injury, poisoning and procedural complications			Drug toxicity, Fall, Injury, Medication error, Nerve injury
Investigations			Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood bilirubin increased, Blood count abnormal, Blood creatinine increased, Blood glucose increased, Blood human chorionic gonadotropin increased, Blood immunoglobulin G increased, Blood

Table 2: Adverse Reactions reported from February 1997 to February 2013			
Body System	**Common (≥ 1% and < 10%)**	**Uncommon (≥ 0.1% and < 1%)**	**Rare (≥ 0.01% and < 0.1%)**
			pressure increased, Blood urea increased, Hematocrit decreased, Hemoglobin decreased, Heart rate decreased, International normalized ratio increased, Laboratory test abnormal, Liver function test abnormal, Neutrophil count decreased, Platelet count decreased, Protein total increased, Weight decreased, Weight increased, White blood cell count decreased, White blood cell count increased
Metabolism and nutrition disorders		Dehydration	Anorexia, Cachexia, Decreased appetite, Diabetes mellitus, Fluid retention, Hypercalcemia, Hyperglycemia, Hyperkalemia, Hypokalemia, Hyponatremia
Musculoskeletal and connective tissue disorders			Arthralgia, Back pain, Bone pain, Joint swelling, Muscle spasms, Muscular weakness, Myalgia, Osteonecrosis, Pain in extremity
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Multiple Myeloma	Acute myeloid leukemia, Myelodysplastic syndrome, Neoplasm malignant, Neoplasm progression
Nervous system disorders	Neuropathy peripheral	Dizziness, Headache, Hypoesthesia, Paresthesia, Somnolence, Syncope, Tremor	Amnesia, Aphasia, Ataxia, Balance disorder, Burning sensation, Cerebral ischemia, Cerebrovascular accident, Coma, Convulsion, Depressed level of consciousness, Dysesthesia, Dysarthria, Dysgeusia, Encephalopathy, Hemorrhage intracranial, Hemiparesis, Hyperesthesia, Lethargy, Loss of consciousness, Memory impairment, Mental impairment, Neuralgia, Neurotoxicity, Paralysis, Peripheral motor neuropathy, Peripheral sensory neuropathy, Polyneuropathy, Sedation, Sensory disturbance, Speech disorder, Transient ischemic attack
Psychiatric disorders		Confusional state	Agitation, Anxiety, Depression, Disorientation, Hallucination, Insomnia, Mental status changes, Nervousness, Thinking abnormal
Renal and urinary disorders		Renal failure	Renal failure acute, Renal failure chronic, Renal impairment, Urinary incontinence
Reproductive system and breast disorders			Amenorrhea, Erectile dysfunction

Table 2: Adverse Reactions reported from February 1997 to February 2013			
Body System	**Common (≥ 1% and < 10%)**	**Uncommon (≥ 0.1% and < 1%)**	**Rare (≥ 0.01% and < 0.1%)**
Respiratory, thoracic and mediastinal disorders		Dyspnea, Pulmonary embolism	Chronic obstructive pulmonary disease, Cough, Dysphonia, Dyspnea exertional, Epistaxis, Hypoxia, Interstitial lung disease, Lung disorder, Lung infiltration, Pharyngolaryngeal pain, Pleural effusion, Pulmonary hypertension, Pulmonary edema, Respiratory disorder, Respiratory failure
Skin and subcutaneous tissue disorders		Rash, Rash generalized	Alopecia, Dermatitis, Dermatitis exfoliative, Dry skin, Erythema, Hyperhidrosis, Petechiae, Pruritus, Rash erythematous, Rash macular, Rash maculo-papular, Rash pruritic, Skin exfoliation, Skin ulcer, Swelling face, Angioedema, Urticaria
Vascular disorders		Deep vein thrombosis	Embolism, Hemorrhage, Hypertension, Hypotension, Orthostatic hypotension, Phlebitis, Thrombosis

[a] All Preferred Terms under System Organ Class of Infections and Infestations (including bacterial, fungal and viral infections) except for rare infections of Public Health interest will be considered listed.

In addition, there have been very rare (< 1/10,000) reports of Tumor Lysis Syndrome, anaphylactic reaction, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis and drug reaction with eosinophilia and systemic symptoms.

Severe infections including sepsis and septic shock, viral infections including hepatitis B and C reactivation resulting in death, and progressive multifocal leukoencephalopathy (PML) have been reported in the post-market experience with thalidomide. Patients should be monitored for severe infections over the course of their treatment.

Arterial Thromboembolic Events:

Cases of arterial thromboembolic events (ATEE), including fatal cases, have been reported in patients treated with thalidomide. These events included principally myocardial infarction, cerebrovascular accident, transient ischemic attack and other arterial thromboembolic events. Risk factors associated with ATEE, in addition to the underlying malignant disease, age ≥ 65 years, and being male, included hyperlipidemia, hypertension, diabetes, obesity, renal disease, and tobacco use (see **WARNINGS AND PRECAUTIONS, Cardiovascular, Thromboembolic Events**).

DRUG INTERACTIONS

Overview

In vitro thalidomide is not a substrate, inhibitor or inducer of cytochrome P450 enzymes. Hence, co-administration of cytochrome P450 substrates or inhibitors with thalidomide is not likely to result in clinically relevant drug-drug interactions.

Drug-Drug Interactions

Table 3: Established or Potential Drug-Drug Interactions with thalidomide			
Proper name	**Ref**	**Effect**	**Clinical comment**
Anxiolytics, hypnotics, antipsychotics, H_1 anti-histamines, opiate derivatives, barbiturates and alcohol	C	Enhance the sedative activity	Caution should be used when thalidomide is given in combination with medicinal products that cause drowsiness. Warn the patient of the potential of increased sedation. Monitor effects of the combination.
Medications known to be associated with peripheral neuropathy (e.g., vincristine, bortezomib)	T	Increase the risk for 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.
Combined hormonal Contraceptives	CTT	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 75 µg of ethinyl estradiol were studied. The results were similar with and without co-administration of THALOMID® 200 mg/day to steady-state levels.	Thalidomide does not interact with hormonal contraceptives. Thalidomide did not impact the PK profile of an oral contraceptive.
Beta blockers, anticholinesterase agents	T	Increase the risk for bradycardia	Due to thalidomide's potential to induce bradycardia, caution should be exercised with medicinal products having the same pharmacodynamic effect

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

The risk of DVT and PE may potentially be increased with the simultaneous use of other agents used in the treatment of MM, such as high dose dexamethasone and erythropoiesis-stimulating agents as well as Hormone Replacement Therapy in menopause.

Hormonal contraceptives are not recommended due to the increased risk of venous thromboembolic disease.

Drug-Food Interactions

THALOMID® is absorbed equally well with or without food.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
THALOMID® may be associated with dizziness and fatigue. Therefore, patients are advised to be cautious when operating machinery, or when driving.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- The capsules should be taken orally as a single dose, regardless of food intake, at about the same time each day.
- THALOMID® (thalidomide capsules) should be taken at bedtime, to reduce the impact of somnolence.
- The capsules should not be broken, chewed, or opened.
- Patients should be instructed to not extensively handle the capsules
- Capsules should be kept in the blister package until it is time to take them unless it is determined by the pharmacist that it is not safe to do so.
- The capsules should be swallowed whole, preferably with water

Recommended Dose and Dosage Adjustment

Patients with previously untreated MM: In combination with melphalan and prednisone, the recommended dose of THALOMID® for patients ≤ 75 years of age is 200 mg/day. For patients > 75 years of age, the recommended dose of THALOMID® is 100 mg/day.

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

Table 4 outlines the starting doses for the MPT regimen used in previously untreated MM patients based on age and blood counts.

Table 4: Starting Doses for MPT Regimen in Previously Untreated Multiple Myeloma

Age (years)	ANC (/µL)		Platelet Count (/µL)	Melphalan[a,b,c]	Prednisone[d]	THALOMID®[e,f]
≤75	≥1,500	AND	≥100,000	0.25 mg/kg daily	2 mg/kg daily	200 mg daily
>75	≥1,500	AND	≥100,000	0.20 mg/kg daily	2 mg/kg daily	100 mg daily
≤75	<1,500 but ≥1,000	OR	<100,000 but ≥50,000	0.125 mg/kg daily	2 mg/kg daily	200 mg daily
>75	<1,500 but ≥1,000	OR	<100,000 but ≥50,000	0.10 mg/kg daily	2 mg/kg daily	100 mg daily

[a] Melphalan dosed once daily on Days 1 to 4 of each 42-day cycle.
[b] Melphalan dosing: reduce by 50% for moderate (creatinine clearance: ≥30 but <50 mL/min) or severe (CrCl: <30mL/min) renal insufficiency
[c] Maximum daily melphalan dose: 24 mg (subjects ≤75 years old) or 20 mg (subjects >75 years old).
[d] Prednisone dosed once daily on Days 1 to 4 of each 42-day cycle.

[e] THALOMID® dosed once daily at bedtime on Days 1 to 42 of each 42-day cycle.
[f] Due to the sedative effect associated with THALOMID®, administration at bedtime is known to generally improve tolerability.
ANC = absolute neutrophil count

Dose Modification or Interruption:

Patients should be monitored on an ongoing basis for: neutropenia, thrombocytopenia, thromboembolic events, hemorrhage, peripheral neuropathy, rash/skin reactions, bradycardia, syncope and somnolence. Dose delay, reduction or discontinuation, may be considered in patients who develop NCI CTC (National Cancer Institute Common Toxicity Criteria) Grade 3 or 4 adverse reactions and/or based on clinical judgment (see Table 6).

Decreased white blood cell counts, including neutropenia, have been reported in association with the clinical use of THALOMID®. 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.

Table 5 outlines the conditions under which a new cycle of MPT was started in patients with previously untreated multiple myeloma.

Table 5: Conditions to be Met Before Starting a New Cycle of MPT in Previously Untreated MM

		Conditions Met			**Conditions Not Met – Delay 1 Week**		
Baseline Hematologic Status		**New Cycle of MPT Started if:**			**After 1 Week Start New Cycle if:**		
ANC (/µL)	**Platelet Count (/µL)**	**ANC (/µL)**	**Platelet Count (/µL)**	**Melphalan-related nonhemato-logic DLT**	**ANC (/µL)**	**Platelet Count (/µL)**	**Reduce melphalan dose**
≥ 1,500	≥ 100,000	≥ 1,500	≥ 100,000	≤ Grade 2	< 1,500 but ≥ 1,000	< 100,000 but ≥ 50,000	50%
					< 1,000[a]	< 50,000 [a]	
≥ 1,500	< 100,000 but ≥ 50,000	≥ 1,500	≥ 50,000	≤ Grade 2	< 1,500 but ≥ 1,000	≥ 50,000	50%
					< 1,000[a]	< 50,000 [a]	
< 1,500 but ≥ 1,000	≥ 100,000	≥ 1,000	≥ 100,000	≤ Grade 2	≥ 1,000	< 100,000 but ≥ 50,000	50%
					< 1,000[a]	< 50,000 [a]	
< 1,500 but ≥ 1,000	< 100,000 but ≥ 50,000	≥ 1,000	≥ 50,000	≤ Grade 2	≥ 1,000 but < 1,500	≥ 50,000	50%
					< 1,000[a]	< 50,000 [a]	

ANC = absolute neutrophil count; DLT = dose-limiting toxicity; M = melphalan; P = prednisone; T = thalidomide.
[a] based upon medical judgment

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.

If the patient experiences any thromboembolic events, treatment must be interrupted and standard anticoagulation therapy started. Once the patient has been stabilized 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 (see Table 6).

Table 6: Dose Modification Instructions for THALOMID® for Dose-limiting Toxicity During a Treatment Cycle in Previously Untreated Multiple Myeloma

Toxicity	THALOMID® Dose Modification
Rash = Grade 3	Stop THALOMID® dosing until the rash resolves to ≤ Grade 1. Decrease dose by one dose level when resumed.
Rash = Grade 4 or blistering; anaphylaxis	Discontinue THALOMID®
Constipation ≥ Grade 3	Initiate bowel regimen and stop THALOMID® dosing until constipation resolves to ≤ Grade 2. Decrease dose by one dose level when resumed.
Thrombosis/embolism ≥ Grade 3	If occurring during aspirin therapy or during a period of inadequate anticoagulation, initiate adequate anticoagulation treatment. Maintain dosing and dose level at the discretion of the treating physician. Discontinue THALOMID® if occurring during adequate anticoagulation treatment (prophylactic dose of anticoagulation therapy with LMWH, heparin or warfarin [Coumadin]).
Hypo/hyperthyroidism ≥ Grade 2	Initiate appropriate medical therapy. Maintain dosing and dose level at the discretion of the treating physician.
Peripheral Neuropathy = Grade 3	Stop THALOMID® until neuropathy resolved to ≤ Grade 1. Decrease dose by one dose level when resumed.
Peripheral Neuropathy = Grade 4	Discontinue THALOMID®
Other ≥ Grade 3 THALOMID®-related AEs	Stop THALOMID® until the AE resolves to ≤ Grade 2. Decrease dose by one dose level when resumed.

AE = adverse event; LMWH = low molecular weight heparin.

Table 7 describes the dose reduction steps for THALOMID®.

Table 7: THALOMID® Dose Reduction Steps in Previously Untreated Multiple Myeloma		
	Days 1 – 42 of Every 42-Day Cycle	
Dose Level	**Age ≤ 75 years**	**Age > 75**
Starting Dose	200 mg daily	100 mg daily
Dose Level -1	100 mg daily	50 mg daily
Dose Level -2	50 mg daily	50 mg every other day
Dose Level -3	50 mg every other day	—

Missed Dose

If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day. Patients should not take 2 doses at the same time.

OVERDOSAGE

Information on overdosage of THALOMID® (thalidomide capsules) is limited. There have been 6 cases of overdose reported to Celgene at doses up to 1000 mg single dose and 300 mg/day chronic dosing. Symptoms included somnolence in the single dose cases and peripheral neuropathy in one chronic case which resolved. There are also 18 reports of accidental or suicidal overdose in the literature. Doses in these cases ranged from 350 mg in a 5-year old patient to 14.4 g of thalidomide with alcohol in a 21-year old patient with a history of attempted suicides. There have been no reported fatalities in doses of up to 14.4 grams, and all patients recovered without reported sequelae. There is no known specific antidote for THALOMID® overdosage and treatment must be symptomatic. In the event of an overdosage, frequent monitoring of the patient's vital signs and blood counts over the following 2 weeks along with close patient monitoring are indicated. Appropriate supportive care to maintain blood pressure and respiratory status should be administered.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of thalidomide is not fully understood. Thalidomide possesses immunomodulatory, anti-inflammatory and anti-angiogenic properties. Available data from in vitro studies and clinical trials suggest that the immunologic effects of this compound can vary substantially under different conditions, but may be related to suppression of excessive tumor necrosis factor-alpha (TNF-α) production and down-modulation of selected cell surface adhesion molecules involved in leukocyte migration. For example, administration of thalidomide has been

reported to decrease circulating levels of TNF-α in patients with ENL; however, it has also been shown to increase plasma TNF-α levels in HIV-seropositive patients. Other anti-inflammatory and immunomodulatory properties of thalidomide may include suppression of macrophage involvement in prostaglandin synthesis, and modulation of interleukin-10 and interleukin-12 production by peripheral blood mononuclear cells. Thalidomide treatment of MM patients is accompanied by an increase in the number of circulating natural killer cells, and an increase in plasma levels of interleukin-2 and interferon-gamma (T cell-derived cytokines associated with cytotoxic activity). Thalidomide was found to inhibit angiogenesis in a human umbilical artery explant model in vitro. The cellular processes of angiogenesis inhibited by thalidomide may include the proliferation of endothelial cells. Thalidomide is also a non-barbiturate centrally active hypnotic sedative.

Pharmacokinetics

Pharmacokinetic data have been collected in studies conducted in healthy subjects.

Table 8: Plasma Pharmacokinetic Parameter Values for THALOMID® Mean (%CV)

Population/ Single Dose	$AUC_{0\infty}$ µg•hr/mL	C_{max} µg/mL	T_{max} (hrs)	Half-life (hrs)	Clearance (L/hr)
Healthy Subjects (n=14)					
50 mg	4.9 (16%)	0.62 (52%)	2.9 (66%)	5.52 (37%)	10.4 (17%)
200 mg	18.9 (17%)	1.76 (30%)	3.5 (57%)	5.53 (25%)	10.9 (17%)
400 mg	36.4 (26%)	2.82 (28%)	4.3 (37%)	7.29 (36%)	11.7 (24%)

Following a single [^{14}C] thalidomide dose in a healthy human study, the observed elimination half-life in plasma for total radioactivity was longer than for thalidomide, suggesting the possible presence of one or more metabolites with longer terminal half-lives than thalidomide. The half-lives of the drug related radioactivity in plasma and whole blood were 144 and 202 hours, respectively.

Absorption: The absolute bioavailability of thalidomide from THALOMID® (thalidomide capsules) has not yet been characterized in humans. Based on the [^{14}C] thalidomide study in human, greater than 90% of the total radioactivity is recovered in urine suggesting good oral absorption. In addition, the capsules are 90% bioavailable relative to an oral PEG solution. The mean time to peak plasma concentrations (T_{max}) of thalidomide ranged from 2.9 to 5.7 hours indicating that thalidomide is slowly absorbed from the gastrointestinal tract. While the extent of absorption (as measured by area under the curve [AUC]) is proportional to dose in healthy subjects, the observed peak concentration (C_{max}) increased in a less than proportional manner (see Table 8). This lack of C_{max} dose proportionality, coupled with the observed increase in T_{max} values, suggests that this may be due to the poor solubility of thalidomide in aqueous media. It suggests a slower rate of absorption of thalidomide at the highest dose.

Co-administration of THALOMID® with a high fat meal causes minor (< 10%) changes in the observed AUC and C_{max} values; however, it causes an increase in T_{max} to approximately 6 hours.

Distribution: In human blood plasma, the geometric mean plasma protein binding was 55% and 66%, respectively, for (+)-(R)- and (-)-(S)-thalidomide. In a pharmacokinetic study of thalidomide in HIV-seropositive adult male patients receiving thalidomide 100 mg/day, thalidomide was detectable in the semen.

Metabolism: In humans, unchanged drug is the predominant circulating component and thalidomide is not metabolized to any significant extent by the liver cytochrome P450 system. Unchanged thalidomide is not eliminated by the kidney to a notable degree (<3.5% of the dose), but is primarily excreted as hydrolytic metabolites in urine. In vitro, thalidomide itself does not appear to be hepatically metabolized to any large extent, but appears to undergo non-enzymatic hydrolysis in plasma to multiple products. Based on in vitro studies, thalidomide is not anticipated to produce drug-drug interactions due to cytochrome P450 inhibition or induction. In a repeat dose study in which four 50 mg capsules of THALOMID® (200 mg dose) was administered to 10 healthy females for 18 days, thalidomide displayed similar pharmacokinetic profiles on the first and last day of dosing. This suggests that thalidomide does not induce or inhibit its own metabolism.

Excretion: As indicated in Table 8 the mean half-life of elimination ranges from approximately 5 to 7 hours following a single dose and is not altered upon multiple dosing. In humans, [^{14}C] thalidomide is primarily excreted in urine (91.9% of the radioactive dose) mainly as hydrolytic metabolites while fecal excretion is minor (< 2% of the dose). Thalidomide itself is excreted by kidneys to a limited extent (<3.5% of the dose).

Special Populations and Conditions

Pediatrics: No pharmacokinetic data are available.

Geriatrics: THALOMID® has been used in clinical trials in patients up to 92 years of age. For patients > 75 years of age, the recommended starting dose of THALOMID® is 100 mg/day (see **WARNINGS AND PRECAUTIONS, Special populations, Geriatrics** and **DOSAGE AND ADMINISTRATION**).

The adverse reaction profile reported in patients > 75 years of age treated with THALOMID® 100 mg daily was similar to the adverse reaction profile observed in patients ≤ 75 years of age treated with THALOMID® 200 mg once daily. However, the overall frequency of serious (such as atrial fibrillation, back pain, and fall) including fatal adverse reactions was higher in patients > 75 years of age treated with THALOMID® 100 mg daily, possibly due to additional co-morbidities and risk factors (see **ADVERSE REACTIONS, Adverse Drug Reactions from Other Clinical Trials**).

Gender: While a comparative trial of the effects of gender on thalidomide pharmacokinetics has not been conducted, examination of the data for thalidomide does not reveal any significant gender differences in pharmacokinetic parameter values.

Race: Pharmacokinetic differences due to race have not been studied.

Hepatic Insufficiency: The pharmacokinetics of thalidomide in patients with hepatic impairment have not been determined.

Renal Insufficiency: The pharmacokinetics of thalidomide in patients with renal impairment have not been determined. In a study with previously untreated MM patients who received THALOMID® (taken as MPT) 33% of subjects receiving MPT had baseline CrCl < 50 mL/min. Considering that pharmacologically active metabolites are eliminated via urine, patients with severe renal impairment should be carefully monitored for adverse events.

Genetic Polymorphism: The pharmacokinetics of thalidomide in patients with genetic polymorphism has not been determined.

HIV-seropositive Patients: There is no apparent significant difference in measured pharmacokinetic parameter values between healthy human subjects and HIV-seropositive patients following single dose administration of a thalidomide capsule which is bioequivalent to THALOMID®.

Patients with Multiple Myeloma: Pharmacokinetics of thalidomide in patients with multiple myeloma have not been fully characterized.

STORAGE AND STABILITY

Store at 15-30º C. Keep out of the reach of children.

SPECIAL HANDLING INSTRUCTIONS

Currently, no published data are available regarding the cutaneous absorption of thalidomide. Most health care institutions recommend that latex gloves be worn while handling chemotherapeutic agents. Health care providers may consider wearing gloves when directly handling THALOMID® (thalidomide capsules), along with standard hand washing. Females who could become pregnant, or who plan to become pregnant can handle THALOMID® capsules if they are using latex gloves.

Repackaging of THALOMID® must only be done on exceptional circumstances. This should only be done by pharmacists.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Table 9: Dosage forms and composition			
Strength	**Color**	**Imprint**	**Non-medicinal ingredients**
50 mg	White opaque	Do Not Get Pregnant woman logo CELGENE 50 mg	pregelatinized starch and magnesium stearate; capsule shell contains gelatin, titanium dioxide and black ink*
100 mg	Tan opaque	Do Not Get Pregnant woman logo CELGENE 100 mg	pregelatinized starch and magnesium stearate; capsule shell contains gelatin, black iron oxide, yellow iron oxide, titanium dioxide, and black ink*
200 mg	Blue opaque	Do Not Get Pregnant woman logo CELGENE 200 mg	pregelatinized starch and magnesium stearate; capsule shell contains gelatin, FD&C blue #2, titanium dioxide, and white ink**

*The 50 mg, and 100 mg and 200 mg capsule shells have black ink which contains shellac and black iron oxide.
** The 200 mg capsule shell has white ink which contains pharmaceutical glaze (modified) in SD-45, titanium dioxide and simethicone.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

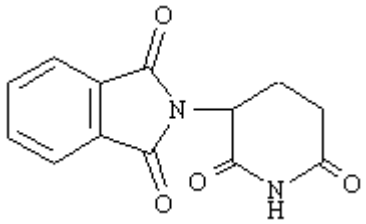
Drug Substance

Proper name: thalidomide

Chemical name: α-(N-phthalimido) glutarimide

Molecular formula and molecular mass: $C_{13}H_{10}N_2O_4$, 258.2 g

Structural formula:



Physicochemical properties: Thalidomide is an off-white to white, odorless, crystalline powder that is soluble at 25°C in dimethyl sulfoxide and sparingly soluble in water and ethanol. The glutarimide moiety contains a single asymmetric center and, therefore, may exist in either of two optically active forms designated S-(-) or R-(+). Thalidomide used in THALOMID® contains an equal mixture of the S-(-) and R-(+) forms and, therefore, has a net optical rotation of zero.

CLINICAL TRIALS

Study IFM 99-06

Study demographics and trial design

The efficacy and safety of THALOMID® (thalidomide capsules) were evaluated in patients with MM in IFM 99-06. This was a randomized, open-label, parallel group, multicenter study comparing thalidomide in combination with melphalan plus prednisone (MPT) versus melphalan plus prednisone (MP) for 12 cycles of 6 weeks in newly diagnosed MM patients. Even though this study had an open-label design, the primary endpoint, Overall Survival (OS), was an objective endpoint.

Patients in the MPT treatment group received thalidomide orally at a starting dose of 200 mg/day increasing to a dose of 400mg/day after 2 to 4 weeks depending on the absence of major adverse events. Melphalan was administered at 0.25 mg/kg/day and prednisone at 2 mg/kg/day from Day 1 to 4 at 6 week intervals for 12 cycles. The MP treatment group used the same melphalan and prednisone dosing schedule as the MPT treatment group. All subjects received bisphosphonates. The demographic characteristics are shown in Table 10.
Visits were planned at 3 months, 6 months, and every 6 months thereafter, until treatment withdrawal or death.

Table 10: Demographic Characteristics – ITT Population (Study IFM 99-06)

Demographic Characteristic	MPT (N = 125)	MP (N = 196)
Age (Years)		
N	125	196
Mean ± Std Dev	69.7 ± 2.9	69.7 ± 2.7
Median	69.2	9.5
Min, Max	64, 76	65, 75
Age Group (Years) – n (%)		
< 70	75 (60)	112 (57)
≥ 70	50 (40)	84 (43)
Gender – n (%)		
Male	63 (50)	109 (56)
Female	62 (50)	87 (44)
Race – n (%)		
Caucasian	124 (>99)	194 (99.0)
Other	0 (0)	2 (1)
Missing	1 (<1)	0 (0)
MM Stage (Durie Salmon) – n (%)		
I	13 (10.4)	18 (9.2)
II	33 (26.4)	50 (25.6)
III	79 (63.2)	127 (65.1)
Missing	0	1 (0.5)
ISS Stage – n (%)		
I	38 (30.4)	61 (31.1)
II	42 (33.6)	67 (34.2)
III	32 (25.6)	54 (27.6)
Missing	13 (10.4)	14 (7.1)

The median duration of thalidomide exposure was 10.5 months and the median thalidomide daily dosing was 217.4 mg (Table 11).

Table 11: Duration of exposure and average daily dose of thalidomide for the MPT group safety population N = 109		
Parameter	**Thalidomide duration in months***	**Thalidomide daily dosing in mg**
Mean** ± SD	9.9 ± 6.1	238.1 ± 99.7
Median	10.5	217.4
Q1, Q3	4.5, 15.2	160.1, 326.0
Min, Max	0.4, 26.9	75.3, 400.0

*Number of months from day of first dose to last dose including interruption period
** Calculated for each subject. Individual means were then used to calculate the treatment group mean and SD
Q1 = 25th percentile; Q3 = 75th percentile; Subjects still receiving THALOMID® on 8 October 2005 were excluded from the calculations

Study results

Overall Survival – ITT Population

Overall survival was defined as the time from randomization to death from any cause. Two analyses are presented. The first cut off was 8 October 2005 while the second was 8 January 2007. For the earlier cut off, for those patients who were alive at the time of analysis (n = 240) or who were lost to follow-up before death was documented (n = 1), OS was censored at the last date that the patient was known to be alive. All censored information corresponded to administrative censoring, except in the case of one patient who was lost to follow-up. For the later cut off, an additional 15 months of follow-up data was obtained. The additional follow-up time provided approximately 30% more deaths (268 deaths compared to 206 deaths) and an increase in median follow-up time of approximately 40% (51.5 months compared to 36.8 months). The statistical methodology and censoring used for this update of OS was identical to that used for the earlier cut off. Table 12 summarizes OS by treatment for the ITT population.

Table 12: Summary of Overall Survival (OS)– ITT Population (Study IFM 99-06)				
OS	**8 October 2005 cut off**		**8 January 2007 cut off**	
	MPT (N=125)	**MP (N=196)**	**MPT (N=125)**	**MP (N=196)**
Died – n (%)	43 (34.4)	97 (49.5)	62 (49.6)	128 (65.3)
Censored – n (%)	82 (65.6)	99 (50.5)	63 (50.4)	68 (34.7)
Follow-up (Months)				
Median	36.8	34.1	51.3	46.9
95% CI	30.0, 43.5	26.8, 41.4	43.8, 58.7	38.5, 55.4
OS Time (Months)				
Median	53.6	32.2	51.6	33.2
95% CI	43.4, 63.8	23.9, 40.5	42.7, 60.4	27.0, 39.4
Hazard Ratio (97.5% CI) [a]	0.56 (0.37, 0.84)	1	0.59 (0.42, 0.84)	1
P-value [b]	0.0012		0.0008	

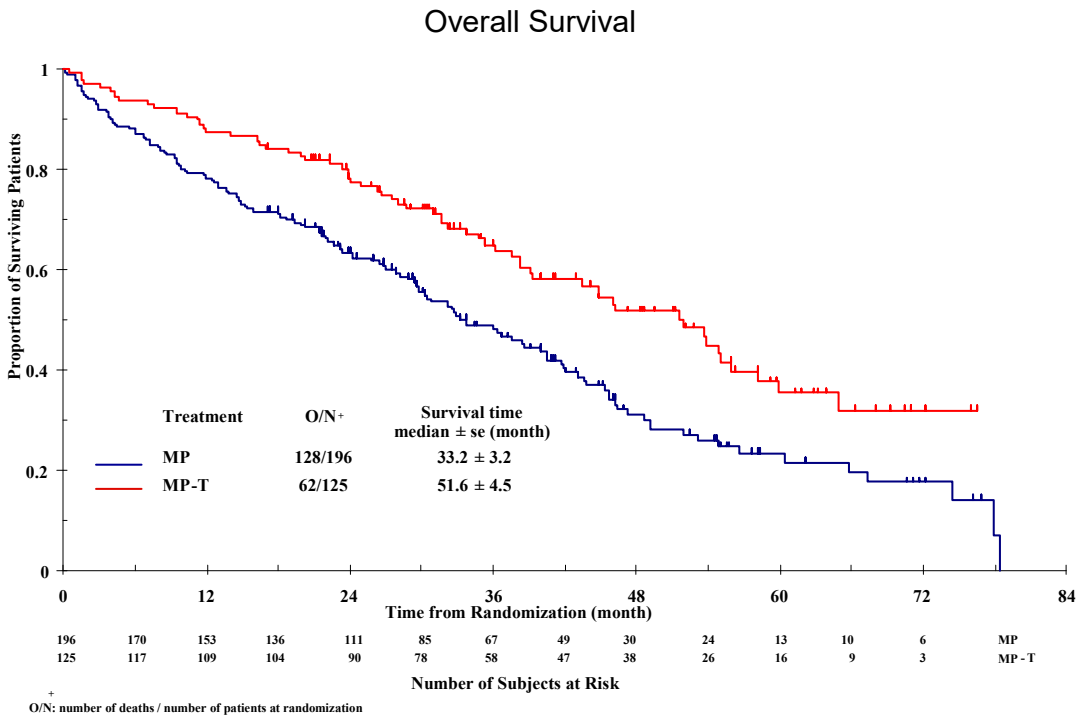
[a] Based on a proportional hazards model comparing the hazard functions associated with treatment groups (MPT:MP)
[b] Based on a two-sided un-stratified log rank test of survival curve differences between treatment groups.

As of 08 Oct 2005, the median follow-up time was 36.8 months, and similar values were obtained across the 2 treatment groups (34.1 and 36.8, months in the MP and MPT treatment groups respectively). These data indicate that sufficient follow-up was available to adequately assess the primary endpoint, OS, for all treatment groups. As of 08 Jan 2007, the reverse Kaplan Meier (KM) median follow-up time was 51.5 months, and similar values were obtained across the treatment groups (51.3 and 46.9 months in the MPT and MP groups, respectively).

Results of these analyses showed that at both the earlier and later cut off, treatment with MPT was superior to MP for prolonging OS, with the median survival increased by 21.4 months at the earlier cut off. At the time of the later cut off, the results are similar with the median survival increased by 18.4 months.

At the time of the earlier cut off, patients in the MPT group had a 44% (p = 0.0012) reduced risk of death relative to patients in the MP treatment group. At the time of the later cut off, as estimated through the proportional hazards model, patients in the MPT group had a 41% (p = 0.0008) reduced risk of death compared to patients in the MP treatment group.
A KM plot of OS by treatment group for the ITT population as of 8 January 2007 is presented in Figure 1.

Figure 1: Updated Overall Survival – ITT Population as of 8 January 2007



KEY: ITT = intent-to-treat; MP = melphalan-prednisone; MPT = melphalan-prednisone plus THALOMID®; N = number of patients at randomization; O = number of deaths; se = standard error. Note: Tick marks on the survival curves indicate a censored time.

The OS rate at 1, 2, 3, and 4 years is presented by treatment for the ITT population in Table 13.

Table 13: Overall Survival (OS) At 1, 2, 3 and 4 Years Per Treatment Group – ITT Population Estimate of the percentage of patients still surviving at the given time point (Study IFM 99-06)		
OS (%)	**MPT (N=125)**	**MP (N=196)**
1 Year – n	99	134
Estimate (%)	87.5	77.7
95% CI	81.6, 93.4	71.7, 83.7
2 Years – n	68	86
Estimate (%)	78.2	62.2
95% CI	70.4, 86.0	54.9, 69.6
3 Years – n	43	44
Estimate (%)	65.1	47.5
95% CI	55.2, 75.1	39.1, 56.0
4 Years – n	20	16
Estimate (%)	55.2	31.1
95% CI	43.5, 66.8	21.3, 40.8

CI = confidence interval; ITT = intent-to-treat; MP = melphalan-prednisone; MPT=melphalan-prednisone plus thalidomide; n=number of subjects at risk; OS = overall survival. Note: This summary excludes any observation that occurred after 08 Oct 2005.

In the ITT population, the OS rate was always higher in MPT group than in MP treatment group at 1, 2, 3, and 4 years.

Progression Free Survival

PFS was defined as the time from randomization to first progression or death from any cause, whichever occurred first. Patients were censored at the last date that the patient was known to be alive without progression. Table 14 summarizes PFS by treatment for the ITT population.

Table 14: Summary of Progression Free Survival Time (PFS) – ITT Population (Study IFM 99-06)		
Parameter	**MPT (N = 125)**	**MP (N = 196)**
Progression Free Survival (PFS)		
Progressed or died– n (%)	67 (53.63)	152 (77.6)
Censored – n (%)	58 (46.4)	44 (22.4)
Overall PFS Time (Months)		
Median	27.6	17.2
95% CI	22.6, 32.6	14.3, 20.2
Hazard Ratio (97.5% CI) [b, c]	0.45 (0.32, 0.62)	1
P-value [a, c]	< 0.0001	

a Based on a two-sided unstratified log rank test of survival curve differences between treatment groups.
b Based on a proportional hazards model comparing the hazard functions associated with treatment groups (MP:MPT)
c MPT:MP comparison
Notes: This summary excludes any observation that occurred after 08 Oct 2005. The median is based on the Kaplan-Meier estimate.

Additional Clinical Trial Results

In an additional study, in patients with previously untreated MM, in which THALOMID® (as MPT) was a comparator arm, patients who were > 75 years of age who received THALOMID® (as MPT) at 100 mg/day as a starting dose (n=188) achieved a median PFS of 19.2 months.

DETAILED PHARMACOLOGY

The precise mechanism of thalidomide action remains unclear. Thalidomide inhibits angiogenesis by blocking responses to basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF), inhibits bone marrow MM cell growth and survival, enhances cell-mediated immunity by directly co-stimulating T cells and increasing the Natural Killer (NK) T cell number, enhances the percentage of NK cells and plasma interleukin (IL)-2 and interferon-gamma (IFN-γ) levels in MM patients responding to thalidomide therapy, modulates various cytokines such as tumor necrosis factor-alpha (TNF-α), and alters adhesion molecule expression.

TOXICOLOGY

Acute toxicity

The acute toxicity profile of thalidomide was evaluated in a study conducted in 1960 by Distillers Biochemicals. Thalidomide was administered to male Albino mice by the oral route at unspecified doses. An oral LD_{50} of > 5000 mg/kg was obtained. Guinea pigs administered a 650 mg/kg oral dose became quiet and sedated; while those administered a 400 mg/kg intramuscular dose exhibited no effects.

Chronic toxicity

The chronic toxicity profile of thalidomide was evaluated in a series of oral toxicology studies up to 13 weeks duration in mice and rats at doses of 30, 300 and 3000 mg/kg/day and up to 52 weeks duration in dogs at doses of 43, 200 and 1000 mg/kg/day.

In mice, mild/moderate centrilobular hepatocellular hypertrophy was observed from 300 mg/kg/day in males (5-fold human exposure) and at 3000 mg/kg/day in females (9-fold human exposure). Increased liver weight was noted at 3000 mg/kg/day in males (13-fold human exposure) and females. In rats, decreased total and free T4 was observed from 300 mg/kg in males (10-fold human exposure) and from 30 mg/kg/day in females (5-fold human exposure). TSH levels were not evaluated. In female dogs, prolongation of the estrus cycle or no estrus, and a dose-related increase in severity of mammary duct dilatation and hyperplasia of the glandular epithelium was noted from 43 mg/kg/day (<1-fold human exposure). Mammary tissue findings were also observed following a 4-week drug-free period. In male dogs, accumulation of ductal bile plugs in canaliculi was seen at 1000 mg/kg/day (4-fold human exposure).

Exposure margins were derived by comparing AUC_{0-t} in animals with AUC_{0-24} in healthy volunteers administered a 200 mg dose of thalidomide.

Combination toxicity

Thalidomide is indicated in combination with melphalan/prednisone. A combination toxicity study was not performed.

Genotoxicity
Thalidomide is not genotoxic (mutagenic or clastogenic) as evaluated by the *in vitro* Ames bacterial (S. typhimurium and E. coli) reverse mutation assay, the in vitro AS52 Chinese hamster ovary xanthine-guanine phosphoribosyl transferase (XPRT) forward mutation assay, and the in vivo mouse micronucleus test.

Carcinogenicity
Two-year carcinogenicity studies were conducted in male and female mice dosed at 100, 1000 and 3000 mg/kg/day, male rats dosed at 20, 160 and 300 mg/kg/day and female rats dosed at 30, 300 and 3000 mg/kg/day. No compound-related tumorigenic effects were observed at the highest dose levels in male and female mice (9 to 14-fold human exposure), and male rats (12-fold human exposure). In female rats, a tumorigenic effect was not observed at 300 mg/kg/day (16-fold human exposure). Survival was significantly reduced at 3000 mg/kg/day (37-fold human exposure) which precluded interpretation of carcinogenicity findings.

Fertility and early embryonic development (segment I)
Fertility studies were conducted in male rabbits at 30, 150 and 500 mg/kg/day and female rabbits at 10, 50 and 100 mg/kg/day. In treated males, there was no change in mating index but a slight reduction in fertility and pregnancy indices was observed at 500 mg/kg/day. Testicular pathological and histopathological effects (mild to moderate degeneration of the germinal epithelium) were also seen in male rabbits at dose levels ≥ 30 mg/kg/day (6.5-fold the 200 mg clinical dose, based on body surface area, BSA). Thalidomide was detected in sperm at all dose levels. In treated females, there were no compound-related effects in mating, fertility and pregnancy indices up to 100 mg/kg/day.

Embryo-fetal development (segment II)
A dose-ranging segment II study was performed wherein pregnant female rabbits were dosed with thalidomide at 10, 20, 60 and 180 mg/kg/day from gestation day 7 to 19. Maternal toxicity was not observed up to doses of 180 mg/kg/day (3-fold human exposure). The no-observed-adverse-effect-level (NOAEL) for reproductive effects was considered to be 20 mg/kg/day (<1-fold human exposure) and is based on decreased mean number of live fetuses, increased mean number of total (early + late) and early resorptions, and increased percent resorbed conceptuses per litter from 60 mg/kg/day. An increased mean number of dead fetuses was noted at 180 mg/kg/day. The NOAEL for embryonic developmental effects was considered to be 20 mg/kg/day as an increased number of fetuses and litters exhibiting congenital malformations was noted at 60 and 180 mg/kg/day.

A pivotal segment II study was not performed as thalidomide is a known human teratogen (see **CONTRAINDICATIONS**).

Pre- and post-natal development (segment III)
Pregnant female rabbits were dosed with thalidomide at 30, 150 and 500 mg/kg/day from gestation day 6 through to lactation day 28. A thalidomide-related increase in abortions was observed from 30 mg/kg/day (6.5-fold the 200 mg clinical dose, based on BSA). Pups born to thalidomide-treated females exhibited reduced viability as an increased number of females with stillborn pups and number of females with all pups dying during post-natal days 1-4 and 5-29

was observed from 30 mg/kg/day. At 150 and 500 mg/kg/day, a decreased number of liveborn pups, an increased number of stillborn pups, an increased number of dead pups found dead, moribound or sacrificed from post-natal days 1 to 49, and a decreased number of surviving pups/litter throughout the pre-weaning period (up to Day 49) was observed. Thalidomide was not associated with delays in post-natal development, including learning and memory functions.

Milk transfer and fetal exposure
In a developmental toxicology study conducted with rabbits, thalidomide, being a lipophilic compound, distributed into milk with concentrations similar to or slightly greater than those observed systemically. Thalidomide was also detected in fetal plasma following administration of the compound to pregnant rabbits.

SAFETY PHARMACOLOGY

Central nervous and respiratory systems
Neurobehavioral assessments were performed in the 13-week rat (30, 300, 3000 mg/kg/day) and 52-week dog (43, 200, 1000 mg/kg/day) repeat-dose toxicity studies. The effect of thalidomide on respiratory rate was evaluated in the 52-week dog study. There were no toxicologically-relevant findings in both studies.

Cardiovascular system
In vitro *I_{Kr} assay.* The effect of thalidomide on hERG tail currents was evaluated in stably transfected HEK-293 cells. At 25 µg/mL (96.8 µM) and 75 µg/mL (290 µM) thalidomide, hERG tail current was inhibited by 23.1% ($p>0.05$) and 31% ($p<0.01$), respectively, when compared with DMSO. The degree of inhibition was not sufficient to calculate an IC_{50} or IC_{25}.

In vitro Purkinje action potential assay. Ventricular Purkinje fibres isolated from male Beagle dogs were treated with 0.125, 1.25, 12.5, 125 µg/mL thalidomide. At 12.5 and 125 µg/mL, a rate-independent reduction in action potential duration (ADP) was observed at 60% repolarization (APD_{60}), and 90% repolarization (APD_{90}). This reduction was statistically significant at 125 µg/mL. The reduction at ADP_{60} was greater than that at ADP_{90} indicating an inhibition of cardiac calcium channel with onset at approximately12.5 µg/mL. A rate-independent decrease in the maximum rate of depolarization was noted at 125 µg/mL.

In vivo cardiovascular safety data. In the 52-week dog repeat-dose toxicity study (43, 200, 1000 mg/kg/day), a dose-dependent and statistically significant decrease in heart rate was observed in females at 200 mg/kg (102 bpm) and 1000 mg/kg/day (98 bpm) when compared with controls (126 bpm). There were no findings in males. In vivo QTc was not evaluated.

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PART III: CONSUMER INFORMATION

PrTHALOMID®

Thalidomide Capsules House Standard

This leaflet is part III of a three-part "Product Monograph" published when THALOMID® (thalidomide capsules) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about THALOMID®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

THALOMID® can only be given to patients who are registered in and meet all conditions of the RevAid® program. RevAid® is a controlled distribution program of THALOMID®.

What the medication is used for:

THALOMID® is used in combination with melphalan and prednisone in the treatment of patients with previously untreated Multiple Myeloma (MM) who are 65 years of age or older.

What THALOMID® does:

THALOMID® is thought to work in multiple ways to stop or slow the growth of cancer cells.

When it should not be used:

Do not take THALOMID® if:

- You are pregnant. Even a single dose (1 capsule of any strength of THALOMID®) taken by a pregnant woman can **cause severe birth defects**.
- You are at risk of becoming pregnant
- You become pregnant during THALOMID® treatment
- You are breastfeeding
- You are a male patient and are unable to follow or comply with the contraceptive measures of the RevAid Program
- You are allergic to thalidomide, lenalidomide or pomalidomide or any of the other ingredients in THALOMID®.

What the medicinal ingredient is:

thalidomide

What the nonmedicinal ingredients are:

Each capsule contains pregelatinized starch and magnesium stearate in a gelatin capsule. The additional composition of the different capsule strengths is provided in the table below.

Summary of dosage forms

Strength	Color	Imprint	Pack size	Non-medicinal ingredients
50 mg	White opaque	CELGENE / 50 mg Do Not Get Pregnant logo	28 capsules	titanium dioxide, black ink
100 mg	Tan opaque	CELGENE / 100 mg Do Not Get Pregnant logo	28 capsules	black iron oxide, yellow iron oxide, titanium dioxide, black ink
200 mg	Blue opaque	CELGENE / 200 mg Do Not Get Pregnant logo	28 capsules	FD&C Blue #2, titanium dioxide, white ink

What dosage forms it comes in:

THALOMID® is available as capsules. Each capsule contains 50 mg, 100 mg or 200 mg of thalidomide.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

THALOMID® should only be prescribed by a doctor experienced in the use of anti-cancer drugs and registered with the RevAid® controlled distribution program.

Serious side effects with the use of THALOMID® include:

- **birth defects (deformed babies), or death of an unborn baby and spontaneous abortion**
- **peripheral neuropathy (damage to peripheral nerves resulting in numbness, tingling, loss of sensation and pain)**
- **blood clots in the veins and arteries**
- **In some cases, a higher risk of liver problems which may lead to death.**
- **severe allergic reaction called anaphylaxis**

THALOMID® is only available under a controlled distribution program called RevAid®.

BEFORE you use THALOMID® talk to your doctor or pharmacist if you:

- are pregnant or are planning to get pregnant
- are breastfeeding
- have blood problems
- have liver problems

- have or have had heart problems (fainting spell (syncope), slow heart beat)
- have had a seizure
- take other medications that make you feel sleepy
- feel numbness, tingling or pain or a burning feeling in your feet or hands
- have a history of hypersensitivity (an allergic reaction) to thalidomide, or any ingredient in THALOMID®. In rare cases, severe allergic reactions (anaphylactic reaction and/or angioedema) have been reported in patients taking THALOMID®. Talk to your doctor immediately if you have symptoms of allergic reactions.
- smoke, have high blood pressure or high cholesterol levels.
- have had previous hepatitis B or C virus infection (a viral infection of the liver).

THALOMID® may cause birth defects. In order to take this drug you must meet the following conditions:

1. Females who can get pregnant:

- Discuss contraception (birth control) with your health care provider.
- Use at least two effective methods of contraception at the same time.
- Use these two effective methods of contraception:
    - For at least 4 weeks before starting THALOMID® treatment
    - During interruptions of THALOMID® treatment
    - During THALOMID® treatment
    - For at least 4 weeks after stopping THALOMID® treatment
- You must have two negative pregnancy tests before starting treatment:
    - The first 7-14 days prior to starting treatment
    - The second within 24 hours of starting treatment.
- You must have negative pregnancy tests during treatment:
    - Once weekly for the first 4 weeks
    - Once every 4 weeks (or once every 2 weeks if your period is irregular) for the duration of treatment and during treatment interruption
- You must have a final pregnancy test 4 weeks after stopping THALOMID®.

2. Males:

- THALOMID® is present in the sperm of males who take this drug. Use a condom every time you have sexual intercourse with a woman who is pregnant or can get pregnant. This must be done even if you have undergone a successful vasectomy. The condom must be used while:
    - You are taking THALOMID®
    - During interruptions of treatment
    - For 4 weeks after stopping THALOMID®
- Do not donate sperm while taking THALOMID® and for 4 weeks after stopping THALOMID®.
- Inform your sexual partner who can get pregnant that:
    - You are taking THALOMID®
    - There is a risk of birth defects, stillbirths, and spontaneous abortions if a fetus is exposed to your sperm.
    - You must use a condom.

You should contact your doctor immediately if you think your female partner becomes pregnant while you are taking THALOMID®.

3. All Patients:

THALOMID® may cause birth defects and any method of birth control can fail. You should contact your doctor immediately if you think you or your female partner may be pregnant. You should also contact your doctor if you miss your period or experience unusual menstrual bleeding.

- Do not give blood while you take THALOMID® and for 4 weeks after stopping THALOMID®.
- Do not share THALOMID® with other people.

Do not take THALOMID® if you are not enrolled in or do not meet the requirements of the RevAid® controlled distribution program.

Second cancers, namely acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), which are types of blood cancer, have been reported in a small number of patients taking THALOMID® in combination with melphalan and prednisone. Patients should talk to their doctors if they have any concerns about their own increased risk of getting other cancers.

THALOMID® is not recommended for use in children under 19 years of age.

If you are older than 75 years of age there is a possibly greater risk for serious side effects of THALOMID®.

THALOMID® causes drowsiness and sleepiness. **Do not** drive or operate machinery until you know how THALOMID® affects you.

Alcohol may increase drowsiness and sleepiness caused by THALOMID®.

INTERACTIONS WITH THIS MEDICATION

Tell your healthcare provider about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. It is possible that THALOMID® and other medicines may affect each other causing serious side effects, especially with sleeping pills, alcohol, antihistamines, hormone replacement therapy, hormonal contraceptives, steroids, drugs that increase the risk of peripheral neuropathy, drugs that increase the risk of bradycardia (slow heart rate), and drugs that increase the production of red blood cells.

The risk of having blood clots is increased if you take hormone replacement therapy or hormonal contraceptives while taking THALOMID®.

Know the medicines you take. To help you keep track of what medicines you take, make a list of them to show your healthcare provider and pharmacist.

PROPER USE OF THIS MEDICATION

How do I take THALOMID®?

- Take THALOMID® exactly as prescribed by your healthcare professional.
- Keep the capsules in the package until you are ready to take them.
- Take the capsules as a single dose before going to bed. This will make you less likely to feel sleepy at other times.
- You should try to take it at about the same time each day.
- Take the capsule directly from the package and place it in your mouth. Do not put the capsule on the counter or onto a dish or other container before taking it.
- Swallow THALOMID® Capsules whole with water.
- Do not break, chew, or open your capsules.

It is important to remember that if you are being assisted with your medication, females who could become pregnant, or who plan to become pregnant can handle THALOMID® capsules if they are using latex gloves.

Will I have to go for tests during treatment with THALOMID®?

You will have regular blood tests during your treatment with THALOMID®. You should have your blood tested about once a month. Your healthcare provider may adjust your dose of THALOMID® or interrupt your treatment based on the results of your blood tests and on your general condition.

Dose:

Capsules should be taken once daily with water at bedtime.

- Patients older than 75 years of age: 100 mg once daily
- Patients 75 years of age or younger: 200 mg once daily

Overdose:

If you think you have taken too much THALOMID®, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

There are two options if you miss a dose:

1. If less than 12 hours have passed since missing a dose, take the dose.
2. If more than 12 hours have passed since missing a dose at the normal time, do not take the dose. Take the next dose at the normal time on the following day. Do **not** take 2 doses at the same time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, THALOMID® can have side effects.

The most common side effects are:

- Changes in your blood cell counts. Your doctor will monitor your blood cell counts during treatment with THALOMID®
- Constipation
- Sleepiness or feeling tired
- Unusual sensation of numbness, tingling, pins and needles, loss of sensation or pain
- Dizziness
- Feeling shaky
- Swelling of your hands and feet
- Nausea
- Rash

The less common side effects are:

- Heart failure, slow heart rate which can be irregular or regular
- Being sick (vomiting), dry mouth, feeling sick (nausea), diarrhea, upper abdominal pain
- Feeling weak, fever, feeling generally unwell, swelling
- Herpes zoster infection, chest infection (pneumonia), mouth infection (oral fungal infection)
- Recurrence (to become active again) of a previous hepatitis B or C infection, which can be fatal in some cases
- Changes of potassium level in your blood
- Back pain

- Abnormal coordination, unsteady, difficulty in walking, state of unconsciousness, memory and thinking ability disorder
- Depression, confusion
- Kidney disease (acute renal failure)
- Problems related to sexual function (unable to engage in sexual intercourse)
- Shortness of breath, sudden pain in your chest or difficulty in breathing (which may be a symptom of blood clots in the lungs called pulmonary embolism), lung disease
- Rash, dryness of the skin
- Pain or swelling in your legs which may be due to blood clots in the veins (thrombosis), low blood pressure

Peripheral Neuropathy

Tell your doctor if you notice any 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, who may reduce the dose or stop your 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 some time after treatment has stopped. It may not go away, or may go away slowly.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Common			
• constipation	√		
• rash			√
• numbness, tingling, or pain or a burning sensation in the feet or hands		√	
• dizziness	√		
Un-common			
• breathing problems, chest pain, arm or leg swelling			√
• severe blood infection (sepsis) accompanied by fever, chills and severe shaking, and possibly complicated by low blood pressure and confusion (septic shock)		√	
• Chest pain spreading to the arms, neck, jaw, back or stomach, feeling sweaty and breathless, feeling sick or vomiting. This may be due to blood clots in the arteries (which may be symptoms of a heart attack/myocardial infarction).			√
• Having difficulty in seeing or speaking, which is temporary. This may be due to a clot in an artery in the brain.			√
• Bleeding or bruising in the absence of injury.		√	
Rare			
• Symptoms of severe allergic reactions (anaphylactic reaction and/or angioedema) such as sudden swelling of the face, lips, tongue; throat problems, breathing or swallowing; severe rash or itching; fainting; very rapid heartbeat			√
• Bloody or black tarry stools			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Very Rare • Symptoms of inflammation of the liver (hepatitis /reactivation of hepatitis B and C virus) itchy skin, jaundice (yellowing of the skin or whites of eyes), fever, tiredness, joint/muscle pain, loss of appetite, nausea and vomiting, pain in the upper right abdomen, pale stools and dark urine			√
• Skin reactions (Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis) red rash across face and body, peeling skin or blistered skin, flat red rash, fever, body aches; (Drug reaction with eosinophilia and systemic symptoms) flu-like symptoms and a rash on the face then an extended rash with a high temperature and swollen glands			√
Unknown • Symptoms of Progressive Multifocal Leukoencephalopathy: vision changes, difficulty speaking, weakness in limbs, change in the way you walk or balance, persistent numbness, decreased or loss of sensation, memory loss or confusion			√

This is not a complete list of side effects. For any unexpected effects while taking THALOMID®, contact your doctor or pharmacist.

HOW TO STORE IT

Store THALOMID® at 15-30°C. Keep out of the reach of children.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- **Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or**
- **Call toll-free at 1-866-234-2345**

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

The information in this document is current as of the last revision date shown below. The most current information can be found at: www.revaid.ca or by contacting the sponsor, Celgene Inc., at 1-888-RevAid1 (1-888-738-2431) or visiting www.celgenecanada.net.

This leaflet was prepared by Celgene Inc.*

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