

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use THALOMID® safely and effectively. See full prescribing information for THALOMID®.

THALOMID® (thalidomide) capsules for oral use  
Initial U.S. Approval: 1998

### WARNING: FETAL RISK AND VENOUS THROMBOEMBOLIC EVENTS

See full prescribing information for complete boxed warning.

#### FETAL RISK

- If thalidomide is taken during pregnancy, it can cause severe birth defects or death to an unborn baby. Thalidomide should never be used by women who are pregnant or who could be pregnant while taking the drug. Even a single dose [1 capsule (regardless of strength)] taken by a pregnant woman during her pregnancy can cause severe birth defects.
- Pregnancy must be excluded before start of treatment. Prevent pregnancy thereafter by the use of two reliable methods of contraception. (5.1)
- THALOMID® (thalidomide) is only available under a restricted distribution program called "S.T.E.P.S.®" (5.2, 17).

#### VENOUS THROMBOEMBOLIC EVENTS

- Significant increased risk of DVT and PE in patients with multiple myeloma receiving THALOMID® (thalidomide) with dexamethasone (5.3).

#### RECENT MAJOR CHANGES

Warnings and Precautions (5.11) 1/12

#### INDICATIONS AND USAGE

- THALOMID in combination with dexamethasone is indicated for the treatment of patients with newly diagnosed multiple myeloma (MM). (1.1)
- THALOMID is indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL). THALOMID is not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis. THALOMID is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence. (1.2)

#### DOSAGE AND ADMINISTRATION

- MM: 200 mg orally once daily. The recommended dose of dexamethasone is 40 mg/day on days 1-4, 9-12, and 17-20 every 28 days. (2.1)
- ENL: 100 to 300 mg/day for an episode of cutaneous ENL. Up to 400 mg/day for severe cutaneous ENL. (2.2)

#### DOSAGE FORMS AND STRENGTHS

Capsules: 50 mg, 100 mg, 150 mg and 200 mg. (3)

#### CONTRAINDICATIONS

- Pregnancy (Boxed Warning, 4.1, 5.1, 5.2, 8.1, 17)
- Demonstrated hypersensitivity to the drug or its components (4.2, 5.14, 6.2)

#### WARNINGS AND PRECAUTIONS

- Fetal Risks: THALOMID® (thalidomide) is a human teratogen and is available only through a restricted distribution program called S.T.E.P.S.® Females of reproductive potential who are sexually active must use acceptable contraception. (Boxed Warning, 4.1, 5.1, 5.2, 8.6, 17)

- Venous Thromboembolic Events: Observe patients for signs and symptoms of thromboembolism. (5.3, 6.1)
- Drowsiness and Somnolence: Instruct patients to avoid situations where drowsiness may be a problem and not to take other medications that may cause drowsiness. (5.4)
- Peripheral Neuropathy: Examine patients at monthly intervals for the first 3 months of thalidomide therapy and periodically thereafter for signs or symptoms of peripheral neuropathy. Consider electrophysiological testing, consisting of measurement of sensory nerve action potential (SNAP) amplitudes at baseline and thereafter every 6 months in an effort to detect asymptomatic neuropathy. (5.5)
- Dizziness and Orthostatic Hypotension: Advise patients to sit upright for a few minutes prior to standing up from a recumbent position. (5.6)
- Neutropenia: Patients may require dose interruption and/or dose reduction. (5.7)
- Increased HIV Viral Load: Measure viral load after the first and third months of treatment and every 3 months thereafter. (5.8)
- Bradycardia: Monitor patients for bradycardia and possible syncope. Dose reduction or discontinuation may be required. (5.9)
- Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Do not resume THALOMID following discontinuation for these reactions. (5.10)
- Seizures: Monitor patients with a history of seizures or at risk for the development of seizures closely for clinical changes that could precipitate acute seizure activity. (5.11)
- Tumor Lysis Syndrome: Monitor patients at risk (e.g., those with high tumor burden prior to treatment) and take appropriate precautions. (5.12)
- Hypersensitivity: Monitor patients for potential hypersensitivity to the drug and its components. (5.14)

#### ADVERSE REACTIONS

- MM: The most common adverse reactions (≥ 20%) are fatigue, hypocalcemia, edema, constipation, neuropathy-sensory, dyspnea, muscle weakness, leukopenia, neutropenia, rash/desquamation, confusion, anorexia, nausea, anxiety/agitation, asthenia, tremor, fever, weight loss, thrombosis/embolism, neuropathy-motor, weight gain, dizziness, and dry skin. (6.1)
- ENL: The most common adverse reactions (≥ 10%) are somnolence, rash, and headache. (6.1)

#### DRUG INTERACTIONS

- Use caution if other drugs which have sedative and hypnotic properties, slow cardiac conduction and/or cause peripheral neuropathy must be used. (7.1, 7.2, 7.3)
- It is not known whether concomitant use of hormonal contraceptives further increases the risk of thromboembolic disease with THALOMID. (5.13, 7.4)

#### USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Discontinue drug or nursing taking into consideration importance of drug to mother. (8.3)
- Safety and effectiveness in pediatric patients below the age of 12 years have not been established. (8.4)

To report SUSPECTED ADVERSE REACTIONS or fetal exposure: contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: January 2012

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## **FULL PRESCRIBING INFORMATION**

### **WARNING: FETAL RISK AND VENOUS THROMBOEMBOLIC EVENTS**

#### **FETAL RISK**

If thalidomide is taken during pregnancy, it can cause severe birth defects or death to an unborn baby. Thalidomide should never be used by women who are pregnant or who could become pregnant while taking the drug. Even a single dose [1 capsule (regardless of strength)] taken by a pregnant woman during her pregnancy can cause severe birth defects.

Because of this toxicity and in an effort to make the chance of fetal exposure to THALOMID® (thalidomide) as negligible as possible, THALOMID® (thalidomide) is approved for marketing only under a special restricted distribution program approved by the Food and Drug Administration. This program is called the “System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.®)”.

You can get the information about THALOMID and the S.T.E.P.S.® program on the Internet at [www.THALOMID.com](http://www.THALOMID.com) or by calling the manufacturer’s toll-free number 1-888-423-5436.

#### **VENOUS THROMBOEMBOLIC EVENTS**

The use of THALOMID® (thalidomide) in multiple myeloma results in an increased risk of venous thromboembolic events, such as deep venous thrombosis and pulmonary embolism. This risk increases significantly when thalidomide is used in combination with standard chemotherapeutic agents including dexamethasone. In one controlled trial, the rate of venous thromboembolic events was 22.5% in patients receiving thalidomide in combination with dexamethasone compared to 4.9% in patients receiving dexamethasone alone (p = 0.002). Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Instruct patients to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Consider thromboprophylaxis based on an assessment of individual patients’ underlying risk factors.

## **1 INDICATIONS AND USAGE**

### **1.1 Multiple Myeloma**

THALOMID in combination with dexamethasone is indicated for the treatment of patients with newly diagnosed multiple myeloma (MM).

### **1.2 Erythema Nodosum Leprosum**

THALOMID is indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL).

THALOMID is not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis.

THALOMID is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence.

## **2 DOSAGE AND ADMINISTRATION**

THALOMID® (THALIDOMIDE) MUST ONLY BE ADMINISTERED IN COMPLIANCE WITH ALL OF THE TERMS OUTLINED IN THE S.T.E.P.S.® PROGRAM. THALOMID® (THALIDOMIDE) MAY ONLY BE PRESCRIBED BY PRESCRIBERS REGISTERED WITH THE S.T.E.P.S.® PROGRAM AND MAY ONLY BE DISPENSED BY PHARMACISTS REGISTERED WITH THE S.T.E.P.S.® PROGRAM.

Drug prescribing to women of childbearing potential should be contingent upon initial and continued confirmed negative results of pregnancy testing.

### **2.1 Multiple Myeloma**

THALOMID is administered in combination with dexamethasone in 28-day treatment cycles. The dose of THALOMID is 200 mg administered orally once daily with water, preferably at bedtime and at least 1 hour after the evening meal. The dose of dexamethasone is 40 mg daily administered orally on days 1-4, 9-12, and 17-20 every 28 days.

Patients who develop adverse reactions such as constipation, somnolence, or peripheral neuropathy may benefit by either temporarily discontinuing the drug or continuing at a lower dose. With the abatement of these adverse reactions, the drug may be started at a lower dose or at the previous dose based on clinical judgment.

### **2.2 Erythema Nodosum Leprosum**

For an episode of cutaneous ENL, THALOMID dosing should be initiated at 100 to 300 mg/day, administered once daily with water, preferably at bedtime and at least 1 hour after the evening meal. Patients weighing less than 50 kilograms should be started at the low end of the dose range.

In patients with a severe cutaneous ENL reaction, or in those who have previously required higher doses to control the reaction, THALOMID dosing may be initiated at higher doses up to 400 mg/day once daily at bedtime or in divided doses with water, at least 1 hour after meals.

In patients with moderate to severe neuritis associated with a severe ENL reaction, corticosteroids may be started concomitantly with THALOMID. Steroid usage can be tapered and discontinued when the neuritis has ameliorated.

Dosing with THALOMID should usually continue until signs and symptoms of active reaction have subsided, usually a period of at least 2 weeks. Patients may then be tapered off medication in 50 mg decrements every 2 to 4 weeks.

Patients who have a documented history of requiring prolonged maintenance treatment to prevent the recurrence of cutaneous ENL or who flare during tapering should be maintained on the minimum dose necessary to control the reaction. Tapering off medication should be attempted every 3 to 6 months, in decrements of 50 mg every 2 to 4 weeks.

### 3 DOSAGE FORMS AND STRENGTHS

THALOMID 50 mg, 100 mg, 150 mg and 200 mg capsules will be supplied through the S.T.E.P.S.<sup>®</sup> program [see *How Supplied/Storage and Handling (16)*].

THALOMID is available in the following capsule strengths:

50 mg capsules [white opaque], imprinted “Celgene/50 mg” with a “Do Not Get Pregnant” logo.  
100 mg capsules [tan], imprinted “Celgene/100 mg” with a “Do Not Get Pregnant” logo.  
150 mg capsules [tan and blue], imprinted “Celgene/150 mg” with a “Do Not Get Pregnant” logo  
200 mg capsule [blue], imprinted “Celgene/200 mg” with a “Do not Get Pregnant” logo.

### 4 CONTRAINDICATIONS

#### 4.1 Pregnancy: [see *Boxed Warning*]

THALOMID can cause fetal harm when administered to a pregnant woman. Thalidomide is contraindicated in pregnant women and women of childbearing potential who are not using acceptable contraception or continually abstaining from heterosexual sexual contact. Thalidomide is a powerful human teratogen, inducing a high frequency of severe and life-threatening birth defects, even after a single dose [see *Boxed Warning*]. Mortality at or shortly after birth has been reported in about 40% of infants. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. If pregnancy occurs during thalidomide treatment, the drug should be discontinued immediately. Under these conditions, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure to THALOMID<sup>®</sup> (thalidomide) must be reported to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.

When there is no satisfactory alternative treatment, women of childbearing potential may be treated with thalidomide provided adequate precautions are taken to avoid pregnancy. Women must abstain continuously from heterosexual sexual contact or use two methods of reliable contraception, including at least one highly effective method (e.g., IUD, hormonal contraception [birth control pills, injections, hormonal patches, vaginal rings or implants], tubal ligation, or partner’s vasectomy) and one additional effective method (e.g., male latex or synthetic condom, diaphragm, or cervical cap). Patients must use their contraceptive method beginning at least 4 weeks prior to initiating treatment with thalidomide, during therapy with thalidomide, and continuing for at least 4 weeks following discontinuation of thalidomide therapy. If hormonal or IUD contraception is medically contraindicated [see *Drug Interactions (7.4)*], two other contraceptive methods may be used simultaneously.

Women of childbearing potential treated with thalidomide should have a pregnancy test (sensitivity of at least 50 mIU/mL). The test should be performed within the 24 hours prior to beginning thalidomide therapy, weekly during the first 4 weeks of thalidomide therapy, and then at 4-week intervals in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding.

#### 4.2 Hypersensitivity

THALOMID is contraindicated in patients who have demonstrated hypersensitivity to the drug and its components.

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Fetal Risks:

Thalidomide is a powerful human teratogen that induces a high frequency of severe and life-threatening birth defects, even after a single dose. Mortality at or shortly after birth has been reported in about 40% of infants. When there is no satisfactory alternative treatment, women of childbearing potential may be treated with thalidomide provided adequate precautions are taken to avoid pregnancy [see *Warnings and Precautions (5.2)*].

Thalidomide is present in semen. Male patients taking thalidomide (including those with vasectomy) who have female partners of childbearing potential must either completely abstain from sexual contact or must always use a latex or synthetic condom during any sexual contact. The risk to the fetus from the semen of male patients taking thalidomide is unknown.

Oral ingestion is the only type of maternal thalidomide exposure known to result in drug-associated birth defects. There are no specific data available regarding the reproductive risks of cutaneous absorption or inhalation of thalidomide; however, women of reproductive potential should avoid contact with THALOMID<sup>®</sup> (thalidomide) Capsules. THALOMID Capsules should be stored in blister packs until ingestion. If there is contact with non-intact thalidomide capsules or the powder contents, the exposed area should be washed with soap and water.

If healthcare providers or other care givers are exposed to body fluids from patients receiving THALOMID (thalidomide) the exposed area should be washed with soap and water. Appropriate precautions should be utilized, such as wearing gloves to prevent the potential cutaneous exposure to THALOMID.

## 5.2 Reproductive Risk and Special Prescribing Requirements (S.T.E.P.S.<sup>®</sup>):

Because of the potential toxicity of THALOMID and to avoid fetal exposure, THALOMID<sup>®</sup> (thalidomide) is only available under a special restricted distribution program called the "S.T.E.P.S.<sup>®</sup> Program". Prescribers and pharmacists registered with the program can prescribe and dispense the product to patients who are registered and meet all the conditions of the "S.T.E.P.S.<sup>®</sup> Program".

Please see the following information for prescribers, female patients, and male patients about this restricted distribution program.

### **S.T.E.P.S.<sup>®</sup> Program Description**

#### **Prescribers**

THALOMID may be prescribed only by licensed prescribers who are registered in the S.T.E.P.S.<sup>®</sup> program and understand the risk of teratogenicity if thalidomide is used during pregnancy.

Major human fetal abnormalities related to thalidomide administration during pregnancy have been documented: amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia, micropinna, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented. Mortality at or shortly after birth has been reported at about 40%.

Effective contraception must be used for at least 4 weeks before beginning thalidomide therapy, during thalidomide therapy including dose interruptions, and for at least 4 weeks following discontinuation of thalidomide therapy. Effective contraception is indicated even in patients with a history of infertility, unless the patient had a hysterectomy or because the patient has been postmenopausal for at least 24 months. Two reliable forms of contraception must be used simultaneously unless the woman agrees to continuous abstinence from heterosexual sexual contact. Women of childbearing potential should be referred to a qualified provider of contraceptive methods, if needed. Sexually mature women who have not undergone a hysterectomy or who have not been postmenopausal for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months) are considered to be women of childbearing potential.

**Before starting treatment**, women of childbearing potential should have a pregnancy test (sensitivity of at least 50 mIU/mL). The test should be performed within the 24 hours prior to beginning thalidomide therapy. A prescription for thalidomide for a woman of childbearing potential must not be issued by the prescriber until a written report of a negative pregnancy test has been obtained by the prescriber.

**Male Patients:** Thalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with women of reproductive potential while he is taking THALOMID and for at least 4 weeks after he stops taking the drug, even if he has undergone a successful vasectomy.

**Once treatment has started**, pregnancy testing should occur weekly during the first 4 weeks of use; then pregnancy testing should be repeated at 4 weeks in women with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding.

If pregnancy does occur during thalidomide treatment, thalidomide must be discontinued immediately.

Any suspected fetal exposure to THALOMID must be reported immediately to the FDA via the MedWatch number at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Instruct patients to take thalidomide only as prescribed and not to share their thalidomide with anyone else.

Instruct patients not to donate blood or semen during therapy or for 4 weeks following discontinuation of thalidomide.

Instruct patients never to give THALOMID to another person and to return any unused capsules to Celgene or their healthcare provider at the end of treatment.

#### **Female Patients**

THALOMID is contraindicated in WOMEN of childbearing potential unless alternative therapies are considered inappropriate AND THE PATIENT MEETS ALL OF THE FOLLOWING CONDITIONS (i.e., she is essentially unable to become pregnant while on thalidomide therapy):

- she understands and can reliably carry out instructions.
- she is capable of complying with the mandatory contraceptive measures, pregnancy testing, patient registration, and patient survey as described in the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.<sup>®</sup>) program.
- she has received both oral and written warnings of the hazards of taking thalidomide during pregnancy and of exposing a fetus to the drug.
- she has received both oral and written warnings of the risk of possible contraception failure and of the need to use two reliable forms of contraception simultaneously, unless she agrees to continuous abstinence from heterosexual sexual contact. Sexually mature women and girls who have not undergone a hysterectomy or who have not been postmenopausal for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months) are considered to be women of childbearing potential.

- she acknowledges, in writing, her understanding of these warnings and of the need for using two reliable methods of contraception for at least 4 weeks prior to beginning thalidomide therapy, during thalidomide therapy, during dose interruptions, and for at least 4 weeks after discontinuation of thalidomide therapy.
- she has had a negative pregnancy test with a sensitivity of at least 50 mIU/mL within the 24 hours prior to beginning therapy.
- if the patient is between 12 and 18 years of age, her parent or legal guardian must have read this material and agreed to ensure compliance with the above.

#### **Male Patients**

Thalidomide may be used in sexually active males only when the PATIENT MEETS ALL OF THE FOLLOWING CONDITIONS:

- he understands and can reliably carry out instructions.
- he is capable of complying with the mandatory contraceptive measures that are appropriate for men, patient registration, and patient survey as described in the *S.T.E.P.S.*<sup>®</sup> program.
- he has received both oral and written warnings of the hazards of taking thalidomide and exposing a fetus to the drug.
- he has received both oral and written warnings of the risk of possible contraception failure and of the presence of thalidomide in semen. He has been instructed that he must either completely abstain from sexual contact with women who are pregnant or able to become pregnant, or must always use a latex or synthetic condom during any sexual contact with women of childbearing potential, while he is taking THALOMID and for at least 4 weeks after he stops taking the drug, even if he has undergone a successful vasectomy.
- he acknowledges, in writing, his understanding of these warnings and of the need to use a latex condom during any sexual contact with women of childbearing potential, even if he has undergone a successful vasectomy. Sexually mature women and girls who have not undergone a hysterectomy or who have not been postmenopausal for at least 24 consecutive months (i.e., who have had menses at any time in the preceding 24 consecutive months) are considered to be women of childbearing potential.
- if the patient is between 12 and 18 years of age, his parent or legal guardian must have read this material and agreed to ensure compliance with the above.

#### **5.3 Venous Thromboembolic Events:**

The use of THALOMID in patients with MM results in an increased risk of venous thromboembolic events, such as deep venous thrombosis and pulmonary embolus. This risk increases significantly when thalidomide is used in combination with standard chemotherapeutic agents including dexamethasone. In one controlled trial, the rate of venous thromboembolic events was 22.5% in patients receiving thalidomide in combination with dexamethasone compared to 4.9% in patients receiving dexamethasone alone ( $p = 0.002$ ). Consider thromboprophylaxis based on an assessment of individual patients' underlying risk factors. Patients and physicians should be observant for the signs and symptoms of thromboembolism. Patients should seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling [*see Boxed Warning*].

#### **5.4 Drowsiness and Somnolence:**

Thalidomide 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 [*see Drug Interactions (7.1)*]. Advise patients 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. Dose reductions may be required.

#### **5.5 Peripheral Neuropathy:**

Thalidomide is known to cause nerve damage that may be permanent. Peripheral neuropathy is a common ( $\geq 10\%$ ) and potentially severe adverse reaction of treatment with thalidomide that may be irreversible. Peripheral neuropathy generally occurs following chronic use over a period of months; however, peripheral neuropathy following relatively short-term use has been reported. The correlation with cumulative dose is unclear. Symptoms may occur some time after thalidomide treatment has been stopped and may resolve slowly or not at all.

Few reports of neuropathy have arisen in the treatment of ENL despite long-term thalidomide treatment. However, the inability clinically to differentiate thalidomide neuropathy from the neuropathy often seen in Hansen's disease makes it difficult to determine accurately the incidence of thalidomide-related neuropathy in ENL patients treated with thalidomide.

Patients should be examined at monthly intervals for the first 3 months of thalidomide 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. Patients should be regularly counseled, questioned, and evaluated for signs or symptoms of peripheral neuropathy. Consideration should be given to electrophysiological testing, consisting of measurement of sensory nerve action potential (SNAP) amplitudes at baseline and thereafter every 6 months in an effort to detect asymptomatic neuropathy. If symptoms of drug-induced neuropathy develop, thalidomide should be discontinued immediately to limit further damage, if clinically appropriate. Usually, treatment with thalidomide should only be reinitiated if the neuropathy returns to baseline status.

Medications known to be associated with neuropathy should be used with caution in patients receiving thalidomide [*see Drug Interactions (7.3)*].

#### **5.6 Dizziness and Orthostatic Hypotension:**

Patients should also be advised that thalidomide 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.

#### 5.7 Neutropenia:

Decreased white blood cell counts, including neutropenia, have been reported in association with the clinical use of thalidomide. Treatment should not be initiated with an absolute neutrophil count (ANC) of  $<750/\text{mm}^3$ . White blood cell count and differential should be monitored on an ongoing basis, especially in patients who may be more prone to neutropenia, such as patients who are HIV-seropositive. If ANC decreases to below  $750/\text{mm}^3$  while on treatment, the patient's medication regimen should be re-evaluated and, if the neutropenia persists, consideration should be given to withholding thalidomide if clinically appropriate.

#### 5.8 Increased HIV Viral Load:

In a randomized, placebo-controlled trial of thalidomide 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.

#### 5.9 Bradycardia:

Bradycardia in association with thalidomide use has been reported. Cases of bradycardia have been reported, some required medical interventions. The clinical significance and underlying etiology of the bradycardia noted in some thalidomide-treated patients are presently unknown. Monitor patients for bradycardia and syncope. Dose reduction or discontinuation may be required.

Medications known to decrease heart rate should be used with caution in patients receiving thalidomide [see *Drug Interactions* (7.2)].

#### 5.10 Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis:

Serious dermatologic reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, which may be fatal, have been reported. THALOMID should be discontinued if a skin rash occurs and only resumed following appropriate clinical evaluation. If the rash is exfoliative, purpuric, or bullous or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, use of THALOMID should not be resumed.

#### 5.11 Seizures:

Although not reported from pre-marketing controlled clinical trials, seizures, including grand mal convulsions, have been reported during post-approval use of THALOMID in clinical practice. Because these events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. Most patients had disorders that may have predisposed them to seizure activity, and it is not currently known whether thalidomide has any epileptogenic influence. During therapy with thalidomide, 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.

#### 5.12 Tumor Lysis Syndrome:

Monitor patients at risk of tumor lysis syndrome (e.g., patients with high tumor burden prior to treatment) and take appropriate precautions.

#### 5.13 Contraceptive Risks:

Some contraceptive methods may pose a higher risk of adverse effects or may be medically contraindicated in some patients treated with THALOMID. Because some patients may develop sudden, severe neutropenia and/or thrombocytopenia, use of an intrauterine device (IUD) or implantable contraception in these patients may carry an increased risk for infection or bleeding either at insertion, removal or during use. Treatment with THALOMID, the presence of an underlying malignancy, and/or use of an estrogen-containing contraceptive can each increase the risk of thromboembolic events. It is not known if these risks of thromboembolic events are additive. However, they should be taken into consideration when choosing contraceptive methods.

#### 5.14 Hypersensitivity:

Hypersensitivity to THALOMID 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.

### 6 ADVERSE REACTIONS

The following adverse reactions are described in detail in other labeling sections:

- Teratogenicity [see *Boxed Warning, Warnings and Precautions* (5.1, 5.2), and *Patient Counseling Information* (17.1)]
- Venous Thromboembolic Events [see *Boxed Warning, Warnings and Precautions* (5.3), and *Patient Counseling Information* (17.2)]
- Drowsiness and Somnolence [see *Warnings and Precautions* (5.4)]
- Peripheral Neuropathy [see *Warnings and Precautions* (5.5)]
- Dizziness and Orthostatic Hypotension [see *Warnings and Precautions* (5.6)]
- Neutropenia [see *Warnings and Precautions* (5.7)]
- Increased HIV Viral Load [see *Warnings and Precautions* (5.8)]
- Bradycardia [see *Warnings and Precautions* (5.9)]
- Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis [see *Warnings and Precautions* (5.10)]
- Seizures [see *Warnings and Precautions* (5.11)]
- Tumor Lysis Syndrome [see *Warnings and Precautions* (5.12)]
- Hypersensitivity [see *Warnings and Precautions* (5.14)]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

### **6.1 Clinical Trials Experience**

Most patients taking thalidomide can be expected to experience adverse reactions.

#### **Teratogenicity:**

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 during the critical period of pregnancy. The critical period 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, thalidomide must not be used at any time during pregnancy.

Because thalidomide is present in the semen of patients receiving the drug, males receiving thalidomide must always use a latex condom during any sexual contact with women of childbearing potential, even if he has undergone a successful vasectomy.

#### **Venous thromboembolic events:**

An increased risk of venous thromboembolic events (such as deep vein thrombosis and pulmonary embolism) has been reported in patients with multiple myeloma treated with thalidomide.

#### **Peripheral neuropathy:**

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

Somnolence, dizziness, and rash are the most commonly observed adverse reactions associated with the use of thalidomide. Adverse event profiles from clinical trials are summarized in the sections that follow.

#### **Adverse Reactions in Multiple Myeloma Controlled Clinical Trials**

The safety analyses were conducted in two controlled clinical studies (Study 1 and Study 2). The safety analysis in Study 1 was conducted on 204 patients who received treatment. Table 1 lists the most common adverse drug reactions ( $\geq 10\%$ ). The most frequently reported adverse reactions were fatigue, hypocalcemia, edema, constipation, sensory neuropathy, dyspnea, muscle weakness, leukopenia, neutropenia, rash/desquamation, confusion, anorexia, nausea, anxiety/agitation, tremor, fever, weight loss, thrombosis/embolism, neuropathy-motor, weight gain, dizziness, and dry skin.

Twenty-three percent of patients (47/204) discontinued due to adverse reactions; 30% (31/102) from the THALOMID/dexamethasone arm and 16% (16/102) from the dexamethasone alone arm.

**Table 1: Adverse Drug Reactions Reported in ≥10% of Patients in the THALOMID/Dexamethasone Arm**

(Study 1 - Safety Population; N=204)

Organ System Class/Preferred Term	Thal + Dex * (N=102)		Dex Alone* (N=102)	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
<b>Metabolic/Laboratory</b>	97 (95)	33 (32)	96 (94)	30 (29)
Hypocalcemia	73 (72)	11 (11)	60 (59)	5 (5)
<b>Neurology</b>	92 (90)	30 (29)	76 (74)	18 (18)
Neuropathy-sensory	55 (54)	4 (4)	28 (28)	1 (1)
Confusion	29 (28)	9 (9)	12 (12)	3 (3)
Anxiety/agitation	26 (26)	1 (1)	14 (14)	3 (3)
Tremor	26 (26)	1 (1)	6 (6)	0 (0)
Neuropathy-motor	22 (22)	8 (8)	16 (16)	5 (5)
Dizziness/ lightheadedness	20 (20)	1 (1)	14 (14)	0 (0)
Depressed level of consciousness	16 (16)	3 (3)	3 (3)	3 (3)
<b>Constitutional Symptoms</b>	91 (89)	19 (19)	84 (82)	16 (16)
Fatigue	81 (79)	17 (17)	72 (71)	13 (13)
Fever	24 (24)	1 (1)	20 (20)	3 (3)
Weight loss	23 (23)	1 (1)	21 (21)	2 (2)
Weight gain	22 (22)	1 (1)	13 (13)	0 (0)
<b>Blood/Bone Marrow</b>	88 (86)	29 (29)	96 (94)	19 (19)
Leukocytes (decreased)	36 (35)	6 (6)	30 (29)	3 (3)
Neutrophils (decreased)	32 (31)	10 (10)	24 (24)	10 (10)
<b>Gastrointestinal</b>	83 (81)	22 (22)	70 (69)	8 (8)
Constipation	56 (55)	8 (8)	29 (28)	1 (1)
Anorexia	29 (28)	4 (4)	25 (24)	2 (2)
Nausea	29 (28)	5 (5)	23 (22)	1 (1)
Mouth dryness	12 (12)	1 (1)	6 (6)	0 (0)
<b>Cardiovascular</b>	70 (69)	37 (36)	60 (59)	21 (21)
Edema	58 (56)	6 (6)	47 (46)	4 (4)
Thrombosis/embolism	23 (22)	21 (21)	5 (5)	5 (5)
<b>Pain</b>	64 (63)	10 (10)	66 (65)	15 (15)
Myalgia	17 (17)	0 (0)	14 (14)	1 (1)
Arthralgia	13 (13)	0 (0)	10 (10)	2 (2)
<b>Pulmonary</b>	52 (51)	19 (19)	51 (50)	20 (20)
Dyspnea	43 (42)	13 (13)	32 (31)	15 (15)
<b>Dermatology/Skin</b>	48 (47)	5 (5)	35 (34)	2 (2)
Rash/desquamation	31 (30)	4 (4)	18 (18)	2 (2)
Dry skin	21 (21)	0 (0)	11 (11)	0 (0)
<b>Hepatic</b>	47 (46)	7 (7)	45 (44)	4 (4)
Bilirubin	14 (14)	2 (2)	10 (10)	2 (2)
<b>Musculoskeletal</b>	42 (41)	9 (9)	41 (40)	14 (14)
Muscle weakness	41 (40)	6 (6)	38 (37)	13 (13)

\*Treatment-emergent adverse reactions reported in ≥10% of patients in THALOMID/dexamethasone arm and with a ≥1% difference in the THALOMID/dexamethasone arm compared to the dexamethasone alone arm.

The safety analysis in Study 2 was conducted on 466 patients who received treatment. Table 2 lists the most common adverse drug reactions (≥ 10%) that were observed. Table 3 lists the most common Grade 3/4 adverse drug reactions (occurring at > 2%) that were observed. The adverse reactions most often reported by patients treated with THALOMID/dexamethasone were constipation, peripheral edema, tremor, asthenia, dizziness and fatigue. Adverse reactions with a frequency at least 2-fold higher in the THALOMID/dexamethasone group than in the placebo/dexamethasone group include constipation, tremor, deep vein thrombosis and peripheral sensory neuropathy.

Twenty-six percent of patients (121/466) discontinued due to adverse events; 37% (86/234) from the THALOMID/dexamethasone arm and 15% (35/232) from the placebo/dexamethasone arm.

**Table 2: Adverse Drug Reactions Reported in ≥10% of Patients in the THALOMID/Dexamethasone Arm**

(Study 2 - Safety Population; N=466)

MedDRA System Organ Class/Preferred Term	Thal/Dex (N=234)* n (%)	Placebo/Dex (N=232)* n (%)
<b>Patients with at least 1 Adverse Reaction</b>	<b>233 (99)</b>	<b>230 (99)</b>
<b>General Disorders and Administration Site Conditions</b>	<b>176 (75)</b>	<b>149 (64)</b>
Edema peripheral	80 (34)	57 (25)
Asthenia	56 (24)	47 (20)
Fatigue	50 (21)	36 (16)
Edema NOS	31 (13)	19 (8)
<b>Gastrointestinal Disorders</b>	<b>162 (69)</b>	<b>149 (64)</b>
Constipation	116 (50)	49 (21)
Nausea	30 (13)	27 (12)
Dyspepsia	27 (11)	21 (9)
<b>Nervous System Disorders</b>	<b>161 (69)</b>	<b>138 (60)</b>
Tremor	62 (26)	29 (12)
Dizziness	51 (23)	32 (14)
Paraesthesia	27 (12)	15 (6)
Peripheral sensory neuropathy	24 (10)	12 (5)
<b>Infections and Infestations</b>	<b>139 (59)</b>	<b>138 (60)</b>
Pneumonia NOS	35 (15)	28 (12)
<b>Psychiatric Disorders</b>	<b>90 (38)</b>	<b>97 (42)</b>
Anxiety	27 (12)	22 (10)
Depression	24 (10)	19 (8)
<b>Metabolism and Nutrition Disorders</b>	<b>96 (41)</b>	<b>89 (38)</b>
Hyperglycemia NOS	36 (15)	32 (14)
<b>Vascular Disorders</b>	<b>92 (39)</b>	<b>53 (23)</b>
Deep vein thrombosis	30 (13)	4 (2)

\*All adverse reactions reported in ≥10% of patients in THALOMID/dexamethasone arm and with a ≥1% difference in proportion of patients between the THALOMID/dexamethasone arm compared to the placebo/dexamethasone arm.

MedDRA = Medical Dictionary for Regulatory Activities; NOS = not otherwise specified.

**Table 3: Grade 3/4 Adverse Drug Reactions Reported in >2% of Patients in the THALOMID/Dexamethasone Arm  
(Study 2 - Safety Population; N=466)**

<b>MedDRA System Organ Class/Preferred Term</b>	<b>THALOMID/Dex (N=234)* n (%)</b>	<b>Placebo/Dex (N=232)* n (%)</b>
<b>Infections and Infestations</b>	<b>50 (21)</b>	<b>36 (16)</b>
Pneumonia NOS	17 (7)	14 (6)
Bronchopneumonia NOS	7 (3)	3 (1)
<b>General Disorders and Administration Site Conditions</b>	<b>44 (19)</b>	<b>26 (11)</b>
Asthenia	11 (5)	4 (2)
<b>Metabolism and Nutrition Disorders</b>	<b>33 (14)</b>	<b>34 (15)</b>
Hypokalemia	7 (3)	3 (1)
<b>Nervous System Disorders</b>	<b>47 (20)</b>	<b>20 (9)</b>
Syncope	8 (3)	1 (<1)
Peripheral neuropathy NOS	8 (3)	0 (0)
Cerebrovascular accident	6 (3)	1 (<1)
<b>Cardiac Disorders</b>	<b>35 (15)</b>	<b>27 (11)</b>
Atrial fibrillation	11 (5)	8 (3)
Myocardial ischemia	6 (3)	2 (1)
<b>Vascular Disorders</b>	<b>42 (18)</b>	<b>14 (6)</b>
Deep vein thrombosis	27 (12)	4 (2)
<b>Gastrointestinal Disorders</b>	<b>26 (11)</b>	<b>22 (10)</b>
Constipation	7 (3)	2 (1)
<b>Investigations</b>	<b>21 (9)</b>	<b>21 (9)</b>
Weight increased	8 (3)	4 (2)
<b>Blood and Lymphatic System Disorders</b>	<b>24 (10)</b>	<b>17 (7)</b>
Neutropenia	8 (3)	6 (3)
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>	<b>27 (12)</b>	<b>13 (6)</b>
Pulmonary embolism	16 (7)	4 (12)
<b>Psychiatric Disorders</b>	<b>19 (8)</b>	<b>8 (3)</b>
Anxiety	5 (2)	3 (1)
Confusional state	5 (2)	2 (1)
<b>Ear and Labyrinth Disorders</b>	<b>6 (3)</b>	<b>0 (0)</b>
Vertigo	5 (2)	0 (0)

\*All Grade 3/4 adverse reactions with >2% of patients in THALOMID/dexamethasone arm and with a higher frequency in the THALOMID/dexamethasone arm compared to the placebo/dexamethasone arm.

MedDRA = Medical Dictionary for Regulatory Activities; NOS = not otherwise specified.

**Less Common Adverse Drug Reactions in Multiple Myeloma Controlled Clinical Trials**

In Study 2, THALOMID in combination with dexamethasone in patients with multiple myeloma, the following adverse drug reactions not described above were reported\*:

**Gastrointestinal disorders:** Vomiting NOS, dry mouth, peritonitis, diverticular perforation

**Nervous system disorders:** Somnolence, hypoesthesia, polyneuropathy NOS, transient ischemic attack

**Respiratory, thoracic, and mediastinal disorders:** Bronchitis NOS

**Psychiatric disorders:** Mood alteration NOS

**Vascular disorders:** Hypotension NOS, orthostatic hypotension

**Cardiac disorders:** Bradycardia NOS

**Eye disorders:** Blurred vision

\* All adverse reactions with  $\geq 3\%$  of patients in THALOMID/dexamethasone arm and with a  $\geq 1\%$  difference in proportion of patients between the THALOMID/dexamethasone arm compared to the placebo/dexamethasone arm. All grade 3/4 and serious adverse reactions reported  $> 2$  patients in THALOMID/dexamethasone arm and with a percentage higher in the THALOMID/dexamethasone arm compared to the placebo/dexamethasone arm have been considered for possible inclusion. In any cases medical judgment has been applied for consideration of causality assessment.

**Adverse Reactions in Erythema Nodosum Leprosum (ENL) Clinical Trials**

Table 4 lists treatment-emergent signs and symptoms that occurred in THALOMID-treated patients in clinical trials in ENL. The most common adverse reactions ( $\geq 10\%$ ) reported in patients with ENL were somnolence, rash, headache. Doses ranged from 50 to 300 mg/day. All adverse reactions were mild to moderate in severity, and none resulted in discontinuation.

**Table 4: Summary of Adverse Events (AEs)  
Reported in Celgene-sponsored Controlled Clinical Trials**

Body System/Adverse Event	All AEs Reported in Patients with ENL		AEs Reported in ≥3 HIV-seropositive Patients	
	50 to 300 mg/day (N=24)	Thalidomide		Placebo (N=35)
		100 mg/day (N=36)	200 mg/day (N=32)	
<b>Body as a Whole</b>	<b>16 (66.7%)</b>	<b>18 (50.0%)</b>	<b>19 (59.4%)</b>	<b>13 (37.1%)</b>
Abdominal pain	1 (4.2%)	1 (2.8%)	1 (3.1%)	4 (11.4%)
Accidental injury	1 (4.2%)	2 (5.6%)	0	1 (2.9%)
Asthenia	2 (8.3%)	2 (5.6%)	7 (21.9%)	1 (2.9%)
Back pain	1 (4.2%)	2 (5.6%)	0	0
Chills	1 (4.2%)	0	3 (9.4%)	4 (11.4%)
Facial edema	1 (4.2%)	0	0	0
Fever	0	7 (19.4%)	7 (21.9%)	6 (17.1%)
Headache	3 (12.5%)	6 (16.7%)	6 (18.7%)	4 (11.4%)
Infection	0	3 (8.3%)	2 (6.3%)	1 (2.9%)
Malaise	2 (8.3%)	0	0	0
Neck pain	1 (4.2%)	0	0	0
Neck rigidity	1 (4.2%)	0	0	0
Pain	2 (8.3%)	0	1 (3.1%)	2 (5.7%)
<b>Digestive System</b>	<b>5 (20.8%)</b>	<b>16 (44.4%)</b>	<b>16 (50.0%)</b>	<b>15 (42.9%)</b>
Anorexia	0	1 (2.8%)	3 (9.4%)	2 (5.7%)
Constipation	1 (4.2%)	1 (2.8%)	3 (9.4%)	0
Diarrhea	1 (4.2%)	4 (11.1%)	6 (18.7%)	6 (17.1%)
Dry mouth	0	3 (8.3%)	3 (9.4%)	2 (5.7%)
Flatulence	0	3 (8.3%)	0	2 (5.7%)
Liver function tests multiple abnormalities	0	0	3 (9.4%)	0
Nausea	1 (4.2%)	0	4 (12.5%)	1 (2.9%)
Oral moniliasis	1 (4.2%)	4 (11.1%)	2 (6.3%)	0
Tooth pain	1 (4.2%)	0	0	0
<b>Hemic and Lymphatic</b>	<b>0</b>	<b>8 (22.2%)</b>	<b>13 (40.6%)</b>	<b>10 (28.6%)</b>
Anemia	0	2 (5.6%)	4 (12.5%)	3 (8.6%)
Leukopenia	0	6 (16.7%)	8 (25.0%)	3 (8.6%)
Lymphadenopathy	0	2 (5.6%)	4 (12.5%)	3 (8.6%)
<b>Metabolic and Endocrine Disorders</b>	<b>1 (4.2%)</b>	<b>8 (22.2%)</b>	<b>12 (37.5%)</b>	<b>8 (22.9%)</b>
Edema peripheral	1 (4.2%)	3 (8.3%)	1 (3.1%)	0
Hyperlipemia	0	2 (5.6%)	3 (9.4%)	1 (2.9%)
SGOT increased	0	1 (2.8%)	4 (12.5%)	2 (5.7%)
<b>Nervous System</b>	<b>13 (54.2%)</b>	<b>19 (52.8%)</b>	<b>18 (56.3%)</b>	<b>12 (34.3%)</b>
Agitation	0	0	3 (9.4%)	0
Dizziness	1 (4.2%)	7 (19.4%)	6 (18.7%)	0
Insomnia	0	0	3 (9.4%)	2 (5.7%)
Nervousness	0	1 (2.8%)	3 (9.4%)	0
Neuropathy	0	3 (8.3%)	0	0
Paresthesia	0	2 (5.6%)	5 (15.6%)	4 (11.4%)
Somnolence	9 (37.5%)	13 (36.1%)	12 (37.5%)	4 (11.4%)
Tremor	1 (4.2%)	0	0	0
Vertigo	2 (8.3%)	0	0	0
<b>Respiratory System</b>	<b>3 (12.5%)</b>	<b>9 (25.0%)</b>	<b>6 (18.7%)</b>	<b>9 (25.7%)</b>
Pharyngitis	1 (4.2%)	3 (8.3%)	2 (6.3%)	2 (5.7%)
Rhinitis	1 (4.2%)	0	0	4 (11.4%)
Sinusitis	1 (4.2%)	3 (8.3%)	1 (3.1%)	2 (5.7%)
<b>Skin and Appendages</b>	<b>10 (41.7%)</b>	<b>17 (47.2%)</b>	<b>18 (56.3%)</b>	<b>19 (54.3%)</b>
Acne	0	4 (11.1%)	1 (3.1%)	0
Dermatitis fungal	1 (4.2%)	2 (5.6%)	3 (9.4%)	0
Nail disorder	1 (4.2%)	0	1 (3.1%)	0
Pruritus	2 (8.3%)	1 (2.8%)	2 (6.3%)	2 (5.7%)
Rash	5 (20.8%)	9 (25.0%)	8 (25.0%)	11 (31.4%)
Rash maculopapular	1 (4.2%)	6 (16.7%)	6 (18.7%)	2 (5.7%)
Sweating	0	0	4 (12.5%)	4 (11.4%)
<b>Urogenital System</b>	<b>2 (8.3%)</b>	<b>6 (16.7%)</b>	<b>2 (6.3%)</b>	<b>4 (11.4%)</b>
Albuminuria	0	3 (8.3%)	1 (3.1%)	2 (5.7%)
Hematuria	0	4 (11.1%)	0	1 (2.9%)
Impotence	2 (8.3%)	1 (2.8%)	0	0

#### Other Adverse Events Observed in ENL Patients

THALOMID in doses up to 400 mg/day has been administered investigational in the United States over a 19-year period in 1465 patients with ENL. The published literature describes the treatment of an additional 1678 patients. To provide a meaningful estimate of the proportion of the individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using a modified COSTART dictionary/terminology. These categories are used in the listing below. All reported events are included except those already listed in the previous table. Due to the fact that these data were collected from uncontrolled studies, the incidence rate cannot be determined. No causal relationship between THALOMID and these events can be conclusively determined at this time. These are reports of all adverse events noted by investigators in patients to whom they had administered thalidomide.

**Body as a Whole:** Abdomen enlarged, fever, photosensitivity, upper extremity pain.

**Cardiovascular System:** Bradycardia, hypertension, hypotension, peripheral vascular disorder, tachycardia, vasodilation.

**Digestive System:** Anorexia, appetite increase/weight gain, dry mouth, dyspepsia, enlarged liver, eructation, flatulence, increased liver function tests, intestinal obstruction, vomiting.

**Hemic and Lymphatic:** ESR decrease, eosinophilia, granulocytopenia, hypochromic anemia, leukemia, leukocytosis, leukopenia, MCV elevated, RBC abnormal, spleen palpable, thrombocytopenia.

**Metabolic and Endocrine:** ADH inappropriate, amyloidosis, bilirubinemia, BUN increased, creatinine increased, cyanosis, diabetes, edema, electrolyte abnormalities, hyperglycemia, hyperkalemia, hyperuricemia, hypocalcemia, hypoproteinemia, LDH increased, phosphorus decreased, SGPT increased.

**Muscular Skeletal:** Arthritis, bone tenderness, hypertonia, joint disorder, leg cramps, myalgia, myasthenia, periosteal disorder.

**Nervous System:** Abnormal thinking, agitation, amnesia, anxiety, causalgia, circumoral paresthesia, confusion, depression, euphoria, hyperesthesia, insomnia, nervousness, neuralgia, neuritis, neuropathy, paresthesia, peripheral neuritis, psychosis.

**Respiratory System:** Cough, emphysema, epistaxis, pulmonary embolus, rales, upper respiratory infection, voice alteration.

**Skin and Appendages:** Acne, alopecia, dry skin, eczematous rash, exfoliative dermatitis, ichthyosis, perifollicular thickening, skin necrosis, seborrhea, sweating, urticaria, vesiculobullous rash.

**Special Senses:** Amblyopia, deafness, dry eye, eye pain, tinnitus.

**Urogenital:** Decreased creatinine clearance, hematuria, orchitis, proteinuria, pyuria, urinary frequency.

#### Other Adverse Events Observed in HIV-seropositive Patients

In addition to controlled clinical trials, THALOMID has been used in uncontrolled studies in 145 patients. Less frequent adverse events that have been reported in these HIV-seropositive patients treated with THALOMID were grouped into a smaller number of standardized categories using modified COSTART dictionary/terminology and these categories are used in the listing below. Adverse events that have already been included in the tables and narrative above, or that are too general to be informative are not listed.

**Body as a Whole:** Ascites, AIDS, allergic reaction, cellulitis, chest pain, chills and fever, cyst, decreased CD4 count, facial edema, flu syndrome, hernia, thyroid hormone level altered, moniliasis, photosensitivity reaction, sarcoma, sepsis, viral infection.

**Cardiovascular System:** Angina pectoris, arrhythmia, atrial fibrillation, bradycardia, cerebral ischemia, cerebrovascular accident, congestive heart failure, deep thrombophlebitis, heart arrest, heart failure, hypertension, hypotension, murmur, myocardial infarct, palpitation, pericarditis, peripheral vascular disorder, postural hypotension, syncope, tachycardia, thrombophlebitis, thrombosis.

**Digestive System:** Cholangitis, cholestatic jaundice, colitis, dyspepsia, dysphagia, esophagitis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, gum disorder, hepatitis, pancreatitis, parotid gland enlargement, periodontitis, stomatitis, tongue discoloration, tooth disorder.

**Hemic and Lymphatic:** Aplastic anemia, macrocytic anemia, megaloblastic anemia, microcytic anemia.

**Metabolic and Endocrine:** Avitaminosis, bilirubinemia, dehydration, hypercholesteremia, hypoglycemia, increased alkaline phosphatase, increased lipase, increased serum creatinine, peripheral edema.

**Muscular Skeletal:** Myalgia, myasthenia.

**Nervous System:** Abnormal gait, ataxia, decreased libido, decreased reflexes, dementia, dysesthesia, dyskinesia, emotional lability, hostility, hypalgesia, hyperkinesia, incoordination, meningitis, neurologic disorder, tremor, vertigo.

**Respiratory System:** Apnea, bronchitis, lung disorder, lung edema, pneumonia (including Pneumocystis carinii pneumonia), rhinitis.

**Skin and Appendages:** Angioedema, benign skin neoplasm, eczema, herpes simplex, incomplete Stevens-Johnson syndrome, nail disorder, pruritus, psoriasis, skin discoloration, skin disorder.

**Special Senses:** Conjunctivitis, eye disorder, lacrimation disorder, retinitis, taste perversion.

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of THALOMID. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Cardiovascular System:** Cardiac arrhythmias including atrial fibrillation, bradycardia, tachycardia, sick sinus syndrome, EKG abnormalities, myocardial infarction.

**Digestive System:** Intestinal perforation, gastrointestinal perforations, intestinal obstruction.

**Metabolic and Endocrine:** Electrolyte imbalance including hypercalcemia or hypocalcemia, hyperkalemia and hypokalemia, hyponatremia, hypothyroidism, increased alkaline phosphatase, tumor lysis syndrome.

**Nervous System:** Changes in mental status or mood including depression and suicide attempts, disturbances in consciousness including lethargy, syncope, loss of consciousness or stupor, seizures including grand mal convulsions and status epilepticus, Parkinson's disease.

**Skin and Appendages:** Erythema multiforme, toxic epidermal necrolysis.

**Hemic and Lymphatic:** Decreased white blood cell counts including neutropenia and febrile neutropenia, changes in prothrombin time, pancytopenia.

**Respiratory System:** Pleural effusion.

**Reproductive System and Breast Disorders:** amenorrhea, sexual dysfunction.

**Immune System Disorders:** Hypersensitivity, angioedema/urticaria.

**Ear and Labyrinthine Disorders:** Hearing impairment/deafness.

**Renal and Urinary Disorders:** Renal failure.

#### **Other Adverse Events in the Published Literature or Reported from Other Sources**

The following additional events have been identified either in the published literature or from spontaneous reports from other sources: acute renal failure, amenorrhea, aphthous stomatitis, bile duct obstruction, carpal tunnel, chronic myelogenous leukemia, diplopia, dysesthesia, dyspnea, enuresis, erythema nodosum, erythroleukemia, foot drop, galactorrhea, gynecomastia, hangover effect, hypomagnesemia, hypothyroidism, lymphedema, lymphopenia, metrorrhagia, migraine, myxedema, nodular sclerosing Hodgkin's disease, nystagmus, oliguria, pancytopenia, petechiae, purpura, Raynaud's syndrome, stomach ulcer, suicide attempt, interstitial lung disease and severe infections (e.g., fatal sepsis including septic shock).

## **7 DRUG INTERACTIONS**

Thalidomide is not a substrate for cytochrome P450 (CYP450) isoenzymes and does not inhibit or induce human CYP450 enzymes in vitro. Therefore, pharmacokinetic drug-drug interactions are not anticipated when thalidomide is coadministered with drugs that are substrates, inhibitors or inducers of cytochrome P450.

### **7.1 Opioids, Antihistamines, Antipsychotics, Anti-anxiety Agents, or Other CNS Depressants (Including Alcohol)**

The use of opioids, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants concomitantly with THALOMID may cause an additive sedative effect and should be avoided.

### **7.2 Drugs which Cause Bradycardia**

The use of drugs which slow cardiac conduction concomitantly with THALOMID may cause an additive bradycardic effect and should be used with caution. Cardiovascular medications which may cause bradycardia include calcium channel blockers, beta blockers, alpha/beta-adrenergic blockers, and digoxin. Non-cardiac drugs that may cause bradycardia include H2 blockers (e.g., famotidine, cimetidine), lithium, tricyclic antidepressants and neuromuscular blockers (succinylcholine).

In 16 healthy men, the pharmacokinetic profile of a single 0.5 mg digoxin dose was similar with and without the coadministration of thalidomide 200 mg/day at steady state levels. The single dose of digoxin had no effect on the pharmacokinetic profile of thalidomide. The safety of long-term concomitant use of THALOMID and digoxin has not been evaluated.

### **7.3 Drugs which Cause Peripheral Neuropathy**

The use of drugs which cause peripheral neuropathy (e.g., bortezomib, amiodarone, cisplatin, docetaxel, paclitaxel, vincristine, disulfiram, phenytoin, metronidazole, alcohol) can cause an additive effect and should be used with caution.

### **7.4 Hormonal Contraceptives**

Hormonal contraceptives increase the risk of thromboembolic disease. It is not known whether concomitant use of hormonal contraceptives further increases the risk of thromboembolic disease with THALOMID.

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 coadministration of thalidomide 200 mg/day to steady-state levels.

### **7.5 Warfarin**

In 13 healthy men, the pharmacokinetic profile and international normalized ratio (INR) of prothrombin time for warfarin, following a single oral dose of 25 mg, were similar with and without the coadministration of thalidomide 200 mg/day at steady-state levels. The single dose of warfarin had no effect on the pharmacokinetic profile of thalidomide.

### **7.6 Drugs That Interfere with Hormonal Contraceptives**

Concomitant use of HIV-protease inhibitors, griseofulvin, modafinil, penicillins, rifampin, rifabutin, phenytoin, carbamazepine, or certain herbal supplements such as St. John's Wort with hormonal contraceptive agents may reduce the effectiveness of the

contraception up to one month after discontinuation of these concomitant therapies. Therefore, women requiring treatment with one or more of these drugs must use two OTHER effective or highly effective methods of contraception while taking thalidomide.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy Category X: [see Boxed Warnings and Contraindications (4.1)]

THALOMID can cause fetal harm when administered to a pregnant woman. Thalidomide is contraindicated in pregnant women and women of childbearing potential who are not using acceptable contraception or who are not continually abstaining from heterosexual sexual contact. THALOMID is a powerful human teratogen, inducing a high frequency of severe and life-threatening birth defects such as amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia, micropinna, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented and mortality at or shortly after birth has been reported in about 40% of infants. Even a single dose taken by a pregnant woman can cause birth defects. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

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. Report any suspected fetal exposure to THALOMID to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.

A pre- and postnatal reproductive toxicity study was conducted in pregnant female rabbits. Compound-related increased abortion incidences and elevated fetotoxicity were observed at the lowest oral dose level of 30 mg/kg/day (approximately 1.5-fold the maximum human dose based upon BSA) and all higher dose levels. Neonatal mortality was elevated at oral dose levels to the lactating female rabbits  $\geq 150$  mg/kg/day (approximately 7.5-fold the maximum human dose based upon BSA). No delay in postnatal development, including learning and memory functions, were noted at the oral dose level to the lactating female rabbits of 150 mg/kg/day (average thalidomide concentrations in milk ranged from 22 to 36  $\mu\text{g/mL}$ ).

### 8.3 Use in Nursing Mothers

It is not known whether thalidomide is excreted in human milk. Thalidomide is excreted in rabbit milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from THALOMID, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### 8.4 Pediatric Use

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

### 8.5 Geriatric Use

One hundred and seventy-six (52%) of 336 patients treated with THALOMID in combination with dexamethasone were  $\geq 65$  of age while 50 (15%) were  $\geq 75$ . Patients  $\geq 65$  years of age on Study 2 had higher incidences of atrial fibrillation, constipation, fatigue, nausea, hypokalemia, deep venous thrombosis, hyperglycemia, pulmonary embolism, and asthenia compared to patients  $< 65$ .

### 8.6 Females and Males of Reproductive Potential

Thalidomide can cause severe birth defects and fetal or infant death if taken during pregnancy. Women of childbearing potential must either abstain continuously from heterosexual sexual contact or use two methods of effective birth control, including at least one highly effective method (e.g., IUD, hormonal contraception, [birth control pills, injections, hormonal patches, vaginal rings or implants] tubal ligation, or partner's vasectomy) and one additional method (e.g., male latex or synthetic condom, diaphragm, or cervical cap), beginning at least 4 weeks prior to initiating treatment with thalidomide, during dose interruptions, during therapy with thalidomide, and continuing for at least 4 weeks following discontinuation of thalidomide therapy. If hormonal or IUD contraception is medically contraindicated (see also Section 7.4, Drug Interactions), two other effective methods may be used simultaneously.

Thalidomide is present in the semen of patients receiving the drug. Males receiving thalidomide must always use a latex or synthetic condom during any sexual contact with women of reproductive potential, during treatment and for 4 weeks after dose interruption and/or cessation of treatment, even if he has undergone a successful vasectomy. The risk to the fetus from the semen of male patients taking thalidomide is unknown.

### 8.7 Renal Impairment

No clinical studies were conducted with THALOMID in patients with mild, moderate or severe renal function. Renal impairment is not expected to influence drug exposure since  $< 3.5\%$  of the dose is excreted in the urine as unchanged drug.

In a study of 6 patients with end-stage renal disease, thalidomide (200 mg/day) was administered on a non-dialysis day and on a dialysis day and blood samples for pharmacokinetics were collected at least 10 hours following the dose. Comparison of concentration-time profiles on a non-dialysis day and during dialysis showed that the mean total clearance increased by a 2.5-fold during hemodialysis. Because the dialysis was performed 10 hours following administration of the dose, the drug-concentration time curves were not statistically significantly different for days patients were on and off of dialysis. In addition, there were no major differences in thalidomide PK between patients with end-stage renal disease and healthy volunteers. Thus, no dosage adjustment is needed for patients with renal impairment or patients on dialysis.

### 8.8 Hepatic Impairment

No clinical studies have been conducted in patients with hepatic impairment.

## 9 DRUG ABUSE AND DEPENDENCE

Physical and psychological dependence has not been reported in patients taking thalidomide; however, as with other tranquilizers/hypnotics, thalidomide has been reported to result in habituation to its soporific effects.

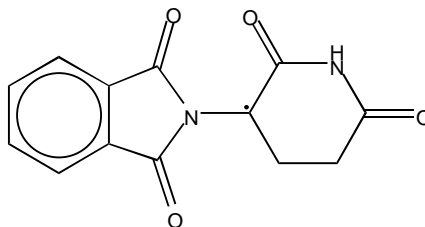
## 10 OVERDOSAGE

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

## 11 DESCRIPTION

THALOMID,  $\alpha$ -(N-phthalimido) glutarimide, is an immunomodulatory agent. The empirical formula for thalidomide is  $C_{13}H_{10}N_2O_4$  and the gram molecular weight is 258.2. The CAS number of thalidomide is 50-35-1.

Chemical Structure of Thalidomide



Note: • = asymmetric carbon atom

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-(+). THALOMID is an equal mixture of the S-(-) and R-(+) forms and, therefore, has a net optical rotation of zero.

THALOMID is available in 50 mg, 100 mg, 150 mg and 200 mg capsules for oral administration. Active ingredient: thalidomide. Inactive ingredients: pregelatinized starch and magnesium stearate. The 50 mg capsule shell contains gelatin, titanium dioxide, and black ink. The 100 mg capsule shell contains black iron oxide, yellow iron oxide, titanium dioxide, gelatin, and black ink. The 150 mg capsule shell contains FD&C blue #2, black iron oxide, yellow iron oxide, titanium dioxide, gelatin, and black and white ink. The 200 mg capsule shell contains FD&C blue #2, titanium dioxide, gelatin, and white ink.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism of action of THALOMID is not fully understood. THALOMID possesses immunomodulatory, antiinflammatory and antiangiogenic 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- $\alpha$ ) 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- $\alpha$  in patients with erythema nodosum leprosum (ENL); however, it has also been shown to increase plasma TNF- $\alpha$  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 multiple myeloma 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.

### 12.3 Pharmacokinetics

#### *Absorption*

Absorption of THALOMID is slow after oral administration. The maximum plasma concentrations are reached approximately 2-5 hours after administration. The absolute bioavailability of thalidomide from thalidomide capsules has not yet been characterized in human subjects due to its poor aqueous solubility. Based on the  $^{14}C$ -radiolabel thalidomide study in human, greater than 90% of the total radioactivity is recovered in urine suggesting good oral absorption. 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 5 below). This lack of  $C_{max}$  dose proportionality, coupled with the observed increase in  $T_{max}$  values, suggests that the poor solubility of thalidomide in aqueous media may be hindering the rate of absorption.

**Table 5: Pharmacokinetic Parameter Values for THALOMID**  
Mean (%CV)

Population/ Single Dose	AUC <sub>0-∞</sub> µg•hr/mL	C <sub>max</sub> µg/mL	T <sub>max</sub> (hrs)	Half-life (hrs)
Healthy Subjects (n=14)				
50 mg	4.9 (16%)	0.62 (52%)	2.9 (66%)	5.52 (37%)
200 mg	18.9 (17%)	1.76 (30%)	3.5 (57%)	5.53 (25%)
400 mg	36.4 (26%)	2.82 (28%)	4.3 (37%)	7.29 (36%)
Patients with Hansen's Disease (n=6)				
400 mg	46.4 (44.1%)	3.44 (52.6%)	5.7 (27%)	6.86 (17%)

Coadministration of THALOMID® (thalidomide) with a high-fat meal causes minor (<10%) changes in the observed AUC and C<sub>max</sub> values; however, it causes an increase in T<sub>max</sub> to approximately 6 hours.

#### **Distribution**

In human 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 subjects receiving thalidomide 100 mg/day, thalidomide was detectable in the semen.

#### **Metabolism**

In a <sup>14</sup>C-radiolabel ADME study in humans, unchanged drug is the predominant circulating component. Thalidomide is not a substrate of the cytochrome P450 system. At therapeutic concentrations, thalidomide is not an inhibitor or inducer of human cytochrome P450 enzymes *in vitro*. Pharmacokinetic drug-drug interactions with substrates, inhibitors or inducers of CYP450 are not anticipated.

#### **Elimination**

The mean elimination half-life of thalidomide in plasma following single oral doses between 50 mg and 400 mg was 5.5 to 7.3 hours. Following a single 400 mg oral dose of radiolabeled thalidomide, the total mean recovery was 93.6% of the administered dose by Day 8. The majority of the radioactive dose was excreted within 48 hours following dose administration. In humans, <sup>14</sup>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). Unchanged thalidomide is not eliminated by the kidney to a notable degree (<3.5% of the dose).

#### **Effects of Weight**

There is a linear relationship between body weight and estimated thalidomide clearance. In MM patients with body weight from 47-133 kg, thalidomide clearance ranged from approximately 6-12 L/h, representing an increase in thalidomide clearance of 0.605 L/h per 10 kg body weight increase.

#### **Effects of Age, Gender and Race**

Analysis of the data from pharmacokinetic studies in healthy volunteers and patients with Hansen's disease ranging in age from 20 to 69 years does not reveal any age-related changes.

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.

Pharmacokinetic differences due to race have not been studied.

#### **Pharmacokinetic Data in Special Populations**

**HIV-seropositive Subjects:** There is no apparent significant difference in measured pharmacokinetic parameter values between healthy human subjects and HIV-seropositive subjects following single-dose administration of THALOMID Capsules.

**Patients with Hansen's Disease:** Analysis of data from a small study in Hansen's patients suggests that these patients, relative to healthy subjects, may have an increased bioavailability of THALOMID. The increase is reflected both in an increased area under the curve and in increased peak plasma levels. The clinical significance of this increase is unknown.

**Pediatric:** No pharmacokinetic data are available in subjects below the age of 18 years.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Two-year carcinogenicity studies were conducted in male and female rats and mice. No compound-related tumorigenic effects were observed at the highest dose levels of 3,000 mg/kg/day to male and female mice (38-fold greater than the highest recommended daily human dose of 400 mg based upon body surface area [BSA]), 3,000 mg/kg/day to female rats (75-fold the maximum human dose based upon BSA), and 300 mg/kg/day to male rats (7.5-fold the maximum human dose based upon BSA).

Thalidomide was neither mutagenic nor genotoxic 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.

Fertility studies were conducted in male and female rabbits; no compound-related effects in mating and fertility indices were observed at any oral thalidomide dose level including the highest of 100 mg/kg/day to female rabbits and 500 mg/kg/day to male rabbits (approximately 5- and 25-fold the maximum human dose, respectively, based upon BSA). Testicular pathological and

histopathological effects (classified as slight) were seen in male rabbits at dose levels  $\geq 30$  mg/kg/day (approximately 1.5-fold the maximum human dose based upon BSA).

## 14 CLINICAL STUDIES

### 14.1 Multiple Myeloma (MM)

The efficacy and safety of THALOMID in patients with multiple myeloma were evaluated in two randomized, multi-center studies (Study 1 and Study 2). Study 1 was an open-label study which randomized 207 symptomatic patients with newly diagnosed MM to THALOMID plus dexamethasone (N = 103) versus dexamethasone alone (N=104). The THALOMID dose was 200 mg daily and the dexamethasone dose was 40 mg orally once daily on days 1-4, 9-12, and 17-20 every 28-days. Each group was treated for four 28-day cycles.

Study 2 randomized 470 newly diagnosed patients with MM to THALOMID plus dexamethasone (N=235) versus placebo plus dexamethasone (N=235). In the THALOMID/dexamethasone arm, a starting dose of thalidomide 50 mg was escalated to 200 mg/day (cycle 2) once daily for 28 days. Patients in both treatment groups took 40 mg of dexamethasone once daily given on days 1-4, 9-12, and 17-20 (every 28 days). Beginning with Cycle 5, the dose of dexamethasone was reduced to 40 mg once daily on Days 1 to 4 of each cycle. Treatment continued as tolerated until disease progression.

Baseline demographics for both studies are presented in Table 6 and disease characteristics for the study population are summarized in Tables 7 (Study 1) and 8 (Study 2).

**Table 6: Baseline Patient Demographics**

Characteristic	Study 1		Study 2	
	THALOMID/ Dexamethasone (N=103)	Dexamethasone (N=104)	THALOMID/ Dexamethasone (N=235)	Placebo/ Dexamethasone (N=235)
<b>Age (years)</b>				
Median	65	68	65	66
Range	37 - 83	38 - 83	39 - 86	31 - 84
<b>Gender<sup>1</sup>, N (%)</b>				
Male	53 (51)	61 (59)	118 (50)	120 (51)
Female	50 (49)	42 (40)	117 (50)	115 (49)
<b>Race<sup>2</sup>, N (%)</b>				
Caucasian	90 (87)	90 (87)	224 (95)	221 (94)
Black	11 (11)	11 (11)	7 (3)	10 (4)
Other	1 (1)	2 (2)	4 (2) <sup>3</sup>	4 (2) <sup>4</sup>

<sup>1</sup>Missing information in Study 1 for 1 patient in the Dex alone group

<sup>2</sup>Missing information in Study 1 for 1 patient per arm

<sup>3</sup>Black/Hispanic [1 (0.4%)], Hispanic [2 (0.9%)], Hispanic/White [1 (0.4%)], Other [0 (0.0%)]

<sup>4</sup>Hispanic [1 (0.4%)], Asian/Pacific Islander [2 (0.9%)], Other [1 (0.4%)]

**Table 7: Baseline Disease Characteristics (Study 1)**

Disease Characteristic	THALOMID/Dexamethasone (N=103)	Dexamethasone alone (N=104)
<b>Stage (Durie-Salmon), N (%)<sup>1</sup></b>		
I	14 (13.6%)	17 (16.3%)
II	47 (45.6%)	44 (42.3%)
III	41 (39.8%)	43 (41.3%)
<b>Immunoglobulin Type, N (%)<sup>2</sup></b>		
IgA	21 (20.4%)	22 (21.2%)
IgG	63 (61.2%)	60 (57.7%)
IgM	0 (0.0%)	1 (1.0%)
Biclonal	0 (0.0%)	1 (1.0%)
<b>Lytic Lesions<sup>3</sup></b>		
None	28 (27.1%)	14 (13.5%)
1-3 lesions	24 (23.3%)	19 (18.3%)
>3 lesions	34 (33.0%)	41 (39.4%)
<b>Serum Light Chain<sup>4</sup></b>		
Kappa	59 (57.3%)	53 (51.0%)
Lambda	28 (27.2%)	40 (38.5%)

<sup>1</sup>Missing information for 1 patient in Thal + Dex arm

<sup>2</sup>Missing information for 19 patients in Thal + Dex arm and 20 patients in Dex alone arm

<sup>3</sup>Missing information for 17 patients in Thal + Dex arm and 30 patients in Dex alone arm

<sup>4</sup>Missing information for 16 patients in Thal + Dex arm and 11 patients in Dex alone arm

Table 8: Baseline Disease Characteristics (Study 2)

Disease Characteristic	THALOMID/ Dexamethasone (N=235)	Placebo/ Dexamethasone (N=235)
<b>Baseline MM Stage (Durie-Salmon), n (%)</b>		
I	2 (1)	2 (1)
II	76 (32)	88 (37)
III	157 (69)	145 (62)
<b>ECOG Performance Status, n (%)</b>		
0	40 (17)	54 (23)
1	124 (53)	112 (48)
2	70 (30)	68 (29)
3	0 (0)	1 (<1)
Missing	1 (<1)	0 (0)
<b>Lytic Bone Lesions, n (%)</b>		
Present	185 (79)	188 (80)
Absent	49 (21)	46 (20)
Missing	1 (<1)	1 (<1)
<b>Bone Marrow Aspirate/Biopsy Cellularity, n (%)</b>		
Normal	102 (43)	108 (46)
Hyperplasia	77 (33)	76 (32)
Hypoplasia	53 (23)	50 (21)
Missing	3 (1)	1 (<1)
<b>Baseline <math>\beta</math>-2 Microglobulin, n (%)</b>		
$\leq$ 2.5 mg/L	33 (14)	35 (15)
$>$ 2.5 mg/L	200 (85)	199 (85)
Missing	2 (1)	1 (<1)

KEY: ECOG=Eastern Cooperative Oncology Group

In Study 1, response rate was the primary endpoint. Response rates based on serum or urine paraprotein measurements were significantly higher in the combination arm (52% vs. 36%). The primary efficacy endpoint in Study 2 was time to progression (TTP), defined as the time from randomization to the first documentation of disease progression, based on the myeloma response criteria. A preplanned interim analysis for Study 2 demonstrated that the combination of THALOMID plus dexamethasone was superior to placebo plus dexamethasone with respect to TTP (Table 9).

Table 9: Summary of Efficacy (Study 2)

	Thalidomide/Dexamethasone (N=235)	Placebo/Dexamethasone (N=235)
<b>Time to Progression</b>		
Progressed – n (%)	72 (31)	126 (54)
Median (Weeks) (95% CI) <sup>a</sup>	97.7 (61.86, NR)	28.3 (27.71, 36.43)
Hazard Ratio (95% CI) <sup>b</sup>	0.43 (0.32, 0.58)	
P-value <sup>c</sup>	<0.0001	
<b>Overall Survival</b>		
Death – n (%)	57 (24)	68 (29)
Median (Weeks) (95% CI) <sup>a</sup>	NR (112.14, NR)	128.6 (113.43, NR)
Hazard Ratio (95% CI) <sup>b</sup>	0.82 (0.57, 1.16)	
<b>Myeloma Response Rate<sup>d</sup> – n (%)</b>		
Complete Response (CR)	18 (8)	6 (3)
Partial Response (PR)	130 (55)	102 (43)
Overall Response (CR + PR)	148 (63)	108 (46)
95% CI (%)	(56, 69)	(39, 53)

<sup>a</sup> The 95% confidence intervals about the median overall TTP, or median overall survival. CI: confidence interval; NR: not reached.

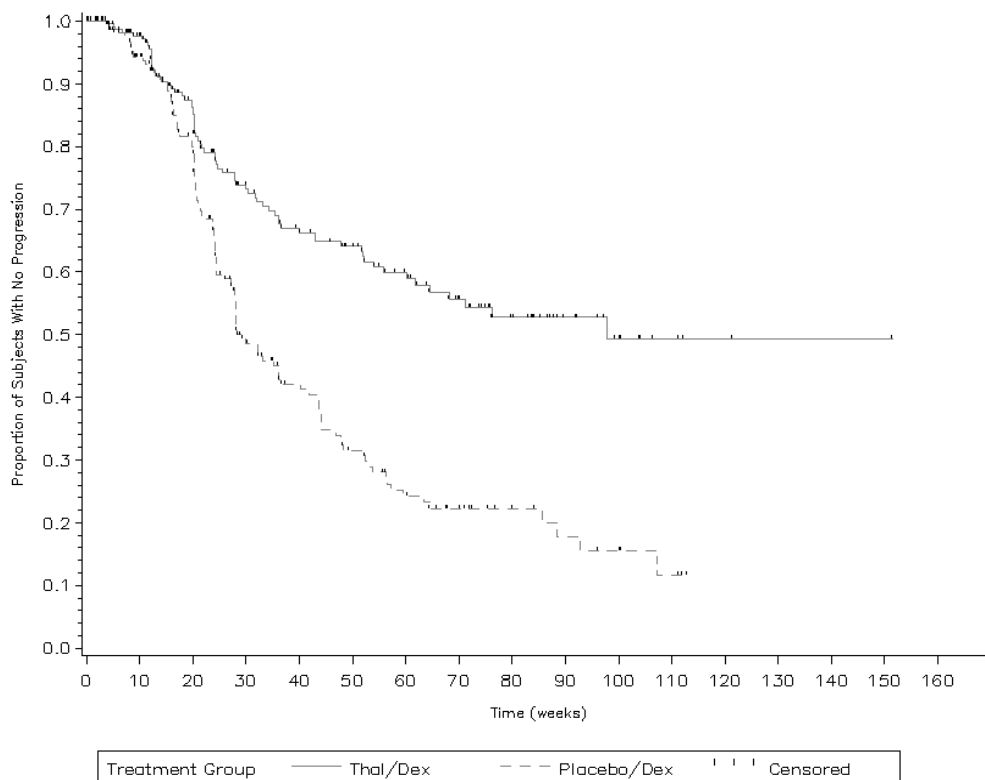
<sup>b</sup> Based on a proportional hazards model comparing the hazard functions associated with treatment groups (thalidomide/dexamethasone:placebo/dexamethasone).

<sup>c</sup> P-value based on the interim analysis was compared with the nominal significance level of 0.0027. Based on a one-sided unstratified log rank test of survival curve differences between treatment groups.

<sup>d</sup> Disease response assessments were determined according to the Bladé criteria. Response is the highest assessment of response during the treatment phase of the study.

The Kaplan-Meier plot of the time to progression by treatment group is presented in Figure 1.

**Figure 1: Kaplan-Meier Plot of Time to Disease Progression**



KEY: Placebo/Dex=placebo/dexamethasone; Thal/Dex=THALOMID/dexamethasone

**14.2. Erythema Nodosum Leprosus (ENL)**

The primary data demonstrating the efficacy of thalidomide in the treatment of the cutaneous manifestations of moderate to severe ENL are derived from the published medical literature and from a retrospective study of 102 patients treated by the U.S. Public Health Service.

Two double-blind, randomized, controlled trials reported the dermatologic response to a 7-day course of 100 mg thalidomide (four times daily) or control. Dosage was lower for patients under 50 kg in weight.

**Table 10: Double-Blind, Controlled Clinical Trials of Thalidomide in Patients with ENL:  
Cutaneous Response**

Reference	No. of Patients	No. Treatment Courses*	Percent Responding**	
			Thalidomide	Aspirin
Iyer <i>et al.</i> Bull World Health Organization 1971;45:719	92	204	75%	25%
Sheskin <i>et al.</i> Int J Lep 1969;37:135	52	173	66%	10%

\* In patients with cutaneous lesions

\*\*Iyer: Complete response or lesions absent

\*\*Sheskin: Complete improvement + “striking” improvement (i.e., >50% improvement)

Waters reported the results of two studies, both double-blind, randomized, placebo-controlled, crossover trials in a total of 10 hospitalized, steroid-dependent patients with chronic ENL treated with 100 mg thalidomide or placebo (three times daily). All patients also received dapsone. The primary endpoint was reduction in weekly steroid dosage.

**Table 11: Double-Blind, Controlled Trial of Thalidomide in Patients with ENL:  
Reduction in Steroid Dosage**

Reference	Duration of Treatment	No. of Patients	Number Responding	
			Thalidomide	Placebo
Waters	4 weeks	9	4/5	0/4
Lep Rev 1971;42:26	6 weeks (crossover)	8	8/8	1/8

Data on the efficacy of thalidomide in prevention of ENL relapse were derived from a retrospective evaluation of 102 patients treated under the auspices of the U.S. Public Health Service. A subset of patients with ENL controlled on thalidomide demonstrated repeated relapse upon drug withdrawal and remission with reinstatement of therapy.

Twenty U.S. patients between the ages of 11 and 17 years were treated with thalidomide, generally at 100 mg daily. Response rates and safety profiles were similar to that observed in the adult population.

Thirty-two other published studies containing over 1600 patients consistently report generally successful treatment of the cutaneous manifestations of moderate to severe ENL with thalidomide.

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## 16 HOW SUPPLIED/STORAGE AND HANDLING

**(THIS PRODUCT IS ONLY SUPPLIED TO PHARMACISTS REGISTERED WITH THE S.T.E.P.S.<sup>®</sup> PROGRAM - See BOXED WARNING)**

THALOMID Capsules are supplied in the following dosages:

50 mg capsules [white opaque], imprinted "Celgene/50 mg" with a "Do Not Get Pregnant" logo.  
Individual blister packs of 1 capsule (NDC 59572-205-17).  
Individual blister packs of 28 capsules (NDC 59572-205-14).  
Boxes of 280 containing 10 prescription packs of 28 capsules each (NDC 59572-205-94).

100 mg capsules [tan], imprinted "Celgene/100 mg" with a "Do Not Get Pregnant" logo.  
Individual blister packs of 28 capsules (NDC 59572-210-15).  
Boxes of 140 containing 5 prescription packs of 28 capsules each (NDC 59572-210-95).

150 mg capsules [tan and blue], imprinted "Celgene/150 mg" with a "Do Not Get Pregnant" logo.  
Individual blister packs of 28 capsules (NDC 59572-215-13).  
Boxes of 112 containing 4 prescription packs of 28 capsules (NDC 59572-215-93).

200 mg capsules [blue], imprinted "Celgene/200 mg" with a "Do Not Get Pregnant" logo.  
Individual blister packs of 28 capsules (NDC 59572-220-16).  
Boxes of 84 containing 3 prescription packs of 28 capsules each (NDC 59572-220-96).

### STORAGE AND DISPENSING

#### PHARMACISTS NOTE:

**BEFORE DISPENSING THALOMID<sup>®</sup>, YOU MUST ACTIVATE THE AUTHORIZATION NUMBER ON EVERY PRESCRIPTION BY CALLING THE CELGENE CUSTOMER CARE CENTER AT 1-888-423-5436 AND OBTAINING A CONFIRMATION NUMBER. YOU MUST ALSO WRITE THE CONFIRMATION NUMBER ON THE PRESCRIPTION. YOU SHOULD ACCEPT A PRESCRIPTION ONLY IF THE AUTHORIZATION NUMBER HAS BEEN ISSUED WITHIN THE PREVIOUS 7 DAYS (TELEPHONE PRESCRIPTIONS ARE NOT PERMITTED); DISPENSE NO MORE THAN A 4-WEEK (28-DAY) SUPPLY. A NEW PRESCRIPTION IS REQUIRED FOR FURTHER DISPENSING. DISPENSE BLISTER PACKS INTACT WITH ENCLOSED PRESCRIBING INFORMATION AND MEDICATION GUIDE (CAPSULES CANNOT BE REPACKAGED); DISPENSE SUBSEQUENT PRESCRIPTIONS ONLY IF FEWER THAN 7 DAYS OF THERAPY REMAIN ON THE PREVIOUS PRESCRIPTION; AND EDUCATE ALL STAFF PHARMACISTS ABOUT THE DISPENSING PROCEDURE FOR THALOMID<sup>®</sup> (thalidomide).**

This drug must not be repackaged.

Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F). [See USP Controlled Room Temperature]. Protect from light.

Rx only and only able to be prescribed and dispensed under the terms of the S.T.E.P.S.<sup>®</sup> Restricted Distribution Program.

Manufactured for Celgene Corporation  
86 Morris Avenue  
Summit, NJ 07901  
1-(888)-423-5436

## 17. PATIENT COUNSELING INFORMATION

See Medication Guide (17.3)

### 17.1 Importance of Preventing Pregnancy

#### Females of Childbearing Potential

Patients must be counseled on thalidomide's risk of teratogenicity. Thalidomide is a known human teratogen that induces a high frequency of severe and life-threatening birth defects. Mortality at or shortly after birth has been reported in about 40% of infants. Thalidomide should never be used by women who are pregnant or who could be pregnant while taking the drug. Even a single dose [1 capsule (regardless of strength)] taken by a pregnant woman during her pregnancy can cause severe birth defects.

THALOMID should only be initiated in women of childbearing potential following a negative pregnancy test. Women of childbearing potential must be informed of the following:

- She must have monthly pregnancy tests
- She must use two different forms of contraception including at least one highly effective form simultaneously during THALOMID® (thalidomide) therapy, and for at least 4 weeks after she has completely finished taking THALOMID® (thalidomide). Highly effective forms of contraception other than tubal ligation include IUD and hormonal (birth control pills, injections, hormonal patches, vaginal rings or implants) and a partner's vasectomy. Additional effective contraceptive methods include male latex or synthetic condom, diaphragm and cervical cap.

Instruct patient to immediately stop taking THALOMID® (thalidomide) and contact her doctor if:

- She becomes pregnant while taking this drug
- If she misses her menstrual period, or experiences unusual menstrual bleeding
- If she stops taking birth control, or if she thinks FOR ANY REASON that she may be pregnant.

Inform the patient that if her doctor is not available, she can call 1-888-668-2528 for information about emergency contraception [see *Use in Specific Populations (8)*].

THALOMID® (thalidomide) treatment should only be initiated in a woman who is not of childbearing potential if she meets at least one of the following criteria:

- She has been postmenopausal naturally for at least 24 months (been through the change of life)
- She has had a hysterectomy or bilateral oophorectomy

For female children not of childbearing potential, the child's parent of guardian certifies that:

- menstruation has not yet begun
- the child will not be engaging in heterosexual contact for at least 4 weeks before THALOMID® (thalidomide) therapy, during therapy, during therapy interruption and for at least 4 weeks after stopping THALOMID® (thalidomide) therapy.

THALOMID® (thalidomide) treatment should only be initiated in a male patient who agrees to:

- either completely abstain from sexual contact with females who are pregnant or able to become pregnant, or use a latex or synthetic condom every time he engages in any sexual contact with females who are pregnant or may become pregnant.
- inform his doctor if he has unprotected sexual contact with a female who can become pregnant.

Inform patient that if his doctor is not available, he can call 1-888-668-2528 for information about emergency contraception.

### 17.2 Venous Thromboembolic Events

THALOMID/dexamethasone has demonstrated significant increased risk of DVT and PE in patients with multiple myeloma [see *Boxed Warning and Warnings and Precautions (5.2)*].

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U.S. Pat. Nos. 5,629,327; 6,045,501; 6,315,720; 6,235,756; 6,561,976; 6,561,977; 6,755,784; 6,869,399; 6,908,432; 7,141,018; 7,230,012; 7,435,745; 7,723,361; 7,874,984 and 7,959,566

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### 17.3 MEDICATION GUIDE

#### MEDICATION GUIDE

THALOMID® (tha-lo-mid)

(thalidomide)

Capsules

Read the Medication Guide that comes with THALOMID before you start taking it and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

#### What is the most important information I should know about THALOMID?

- Before you begin taking THALOMID, you must read and agree to all of the instructions in the *S.T.E.P.S.*® program.
- **THALOMID can cause severe and life-threatening human birth defects (deformed babies) or death of an unborn baby. Females who are pregnant or who plan to become pregnant must not take THALOMID.**

#### Females must not become pregnant:

- for at least 4 weeks before starting THALOMID
- during any breaks (interruptions) in your treatment with THALOMID
- while taking THALOMID
- for at least 4 weeks after stopping THALOMID

**Talk to your healthcare provider right away if you have unprotected sex or if you think your birth control has failed. If your healthcare provider is not available, you can call 1-888-668-2528 for emergency contraception information.**

**If you become pregnant while taking THALOMID, stop taking it right away and call your healthcare provider.**

Healthcare providers and patients should report all pregnancies to:

- FDA MedWatch at 1-800-FDA-1088, and
- Celgene Corporation at 1-888-423-5436

**Males should know that THALOMID passes into semen or sperm.**

- Males, including those who have had a vasectomy, must use a latex or synthetic condom during any sexual contact with a pregnant female or a female that can become pregnant, while taking THALOMID, and for 4 weeks after stopping THALOMID.
- Do not have unprotected sexual contact with a female who is or could become pregnant. Tell your healthcare provider if you do have unprotected sexual contact with a female who is or could become pregnant.
- Do not donate sperm while taking THALOMID, and for 4 weeks after stopping THALOMID. If a female becomes pregnant with your sperm, the baby may be exposed to THALOMID and may be born with birth defects.

**Men, if your female partner becomes pregnant, you should call your healthcare provider right away.**

- **Venous thromboembolism (blood clots).** If you are taking THALOMID in combination with dexamethasone to treat multiple myeloma you have an increased risk for blood clots in your veins and lungs. Call your healthcare provider or get medical help right away if you get any of these signs or symptoms:
  - shortness of breath
  - chest pain
  - arm or leg swelling

### **What is THALOMID?**

THALOMID is a prescription medicine taken, with the medicine dexamethasone, to treat people who have been newly diagnosed with multiple myeloma. Multiple myeloma is a cancer of plasma cells. Plasma cells are found in the bone marrow. Normal plasma cells produce proteins called antibodies. Some antibodies can attack and kill disease-causing germs. People with multiple myeloma may have low blood cell counts and immune problems, giving them a higher risk for getting infections such as pneumonia. They may also have bone pain and breaks (fractures).

THALOMID is also used to treat people when new lesions of leprosy flare up. THALOMID is not used by itself to treat the skin lesions when there is moderate to severe nerve pain. THALOMID is used as a treatment to keep the lesions in check or to prevent the skin lesions of leprosy from coming back (recurring).

It is not known if THALOMID is safe and effective in children under 12 years of age.

### **Who should not take THALOMID?**

- **Do not take THALOMID if you are pregnant, plan to become pregnant, or become pregnant during THALOMID treatment.** See “What is the most important information I should know about THALOMID?”
- **Do not take THALOMID if you are a female who may become pregnant and are not using 2 forms of birth control or are not continually abstaining from sexual contact with a male.** See “How should I take THALOMID?”
- **Do not take THALOMID if you are allergic to anything in it.** See the end of this Medication Guide for a complete list of ingredients in THALOMID.

### **What should I tell my healthcare provider before taking THALOMID?**

Before you take THALOMID, tell your healthcare provider if you:

- have a history of seizures
- drink alcohol
- plan to have surgery
- **are pregnant or breastfeeding.** THALOMID must not be used by women who are pregnant or breastfeeding. See “What is the most important information I should know about THALOMID?” It is not known if THALOMID passes into your breast milk and harms your baby.

**Tell your healthcare provider about all the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements.** THALOMID and other medicines may affect each other causing serious side effects.

Certain medicines can affect the way that birth control pills, injections, patches, or implants work. You could become pregnant.

Especially tell your healthcare provider if you also take:

- a pain medicine
- antihistamines
- a medicine for psychoses
- a medicine for anxiety
- a medicine for your heart
- a medicine for depression
- famotidine (Pepcid, Duexis)
- cimetidine (Tagamet)
- lithium (lithobid)
- bortezomib (Velcade)
- amiodarone (Cordarone, Pacerone)
- cisplatin
- paclitaxel (Abraxane)
- vincristine

- disulfiram (Antabuse)
- metronidazole (Flagyl, Metrocream, Metro lotion, Metrogel, Helidac, Noritate, Plera)
- a penicillin antibiotic
- an anti-HIV medicine
- phenytoin (Fosphenytoin, Cerebyx, Dilantin-125, Extended Phenytoin Sodium, Prompt Phenytoin Sodium, Phenytek, Dilantin, Phenytoin Sodium)
- carbamazepine (Carbatrol, Equetro, Tegretol, Tegretol-XR, Teril, Eptol)
- rifampin (Rifater, Rifamate, Rimactane, Rifadin)
- the herbal supplement St. John's Wort (*Hypericum perforatum*)
- modafinil (Nuvigil, Provigil)
- griseofulvin (Grifulvin V, Gris-Peg)

Ask your healthcare provider if you are not sure if your medicine is one of these.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist.

### **How should I take THALOMID?**

Take THALOMID exactly as prescribed and follow all the instructions of the *S.T.E.P.S.* program.

Before prescribing THALOMID, your healthcare provider will:

- explain the *S.T.E.P.S.* program to you
- have you sign the Patient-Physician Agreement Form
- Keep THALOMID in the blister pack until you take your daily dose.
- Swallow THALOMID capsules whole with water.
- THALOMID is taken one time each day, at least 1 hour after your evening meal. Bedtime is the preferred time to take THALOMID.
- Do not open the THALOMID capsules or handle them any more than needed. If you touch a broken THALOMID capsule or the medicine in the capsule, wash the area of your body with soap and water.
- If you miss a dose of THALOMID and it has been less than 12 hours since your regular time, take it as soon as you remember. If it has been more than 12 hours, just skip your missed dose. Do **not** take 2 doses at the same time.
- If you take too much THALOMID or overdose, call your healthcare provider or poison control center right away.

Females who can become pregnant:

- will have pregnancy tests weekly for 4 weeks, then every 4 weeks if your menstrual cycle is regular, or every 2 weeks if your menstrual cycle is irregular.

If you miss your period or have unusual bleeding, you will need to have a pregnancy test and receive counseling.

- must agree to use 2 different forms of effective birth control at the same time, for at least 4 weeks before, while taking, and for at least 4 weeks after stopping THALOMID®.

Males who take THALOMID, even those who have had a vasectomy, must agree to use a latex or synthetic condom during sexual contact with a pregnant female or a female who can become pregnant.

### **What should I avoid while taking THALOMID?**

- **Females: Do not get pregnant and do not breastfeed while taking THALOMID.**

**Males: Do not donate sperm.** See “What is the most important information I should know about THALOMID?”, “Who should not take THALOMID?”, and “What should I avoid while taking THALOMID?”

- **Do not share THALOMID® with other people.** It may cause birth defects and other serious problems.

- **Do not donate blood** while you take THALOMID, and for 4 weeks after stopping THALOMID. If someone who is pregnant gets your donated blood, her baby may be exposed to THALOMID and may be born with birth defects.
- THALOMID can cause dizziness and drowsiness. Avoid drinking alcohol, operating machinery, and driving a car when taking THALOMID. Avoid taking other medicines that may cause drowsiness without talking to your healthcare provider first.

**What are the possible side effects of THALOMID?**

**THALOMID may cause serious side effects, including:**

- See “What is the most important information I should know about THALOMID?”
- **Drowsiness and sleepiness.** See “What should I avoid while taking THALOMID?”
- **Nerve damage.** Nerve damage is common with THALOMID. If the nerve damage is severe, it may not go away. Stop taking THALOMID and call your healthcare provider right away if you have any of these early symptoms of nerve damage in your hands, legs, or feet:
  - numbness
  - tingling
  - pain
  - burning sensation
- **Dizziness and decreased blood pressure when changing positions.** THALOMID may cause a decrease in your blood pressure, and you may feel dizzy when you go from a lying down or sitting position to standing up. When changing positions, sit upright for a few minutes before standing to help prevent this.
- **Decreased white blood cell count.** THALOMID can cause decreased white blood cell counts, including neutrophils. Neutrophils are a type of white blood cell that is important in fighting bacterial infections. Your healthcare provider should check your white blood count before and regularly while you take THALOMID. If your neutrophils are too low you should not start THALOMID and if they are low during treatment, your dose of THALOMID may need to be changed.
- **Increased HIV virus in the blood.** If you are HIV positive, your healthcare provider should check your viral load after one month and three months of treatment, then every 3 months after that.
- **Slow heartbeat (bradycardia).** Tell your healthcare provider if you have a slow heartbeat, fainting, dizziness or shortness of breath.
- **Serious skin reactions.** Serious skin reactions can happen with THALOMID and may cause death. Call your healthcare provider right away if you have any skin reaction while taking THALOMID.
- **Seizures.** Tell your healthcare provider right away if you have a seizure while taking THALOMID.
- **Tumor Lysis Syndrome (TLS).** TLS is caused by a fast breakdown of cancer cells. TLS can cause a build up of potassium, phosphorus, uric acid, and low calcium levels in your blood. This can cause you to have serious kidney problems, an abnormal heart beat and can cause death. Your healthcare provider will check your blood for these problems.
- **Birth control.** Certain birth control methods may pose a higher risk of serious side effects and should not be used in some women. These risks include severe decreased white blood cell count, low platelet counts, and blood clots. Use of an intrauterine device (IUD) or implantable birth control may also increase your risk of infection or bleeding during insertion, removal or during use of the device.
- **Allergic reaction.** Allergic reactions can happen with THALOMID and may be severe. Call your healthcare provider or get medical help right away if you have any of these symptoms of allergic reaction:
  - a red, itchy rash
  - fever
  - fast heartbeat
  - feel dizzy or faint

The most common side effects of THALOMID for treatment of multiple myeloma include:

- tiredness
- decreased calcium levels
- swelling of the hands and feet
- constipation
- numbness or tingling
- muscle weakness
- skin rash or peeling
- confusion
- decreased appetite
- nausea
- anxiety
- decreased energy or strength

- tremor
- fever
- weight loss
- muscle twitching and cramping
- weight gain
- dizziness
- dry skin

The most common side effects THALOMID for treatment of leprosy include:

- sleepiness
- rash
- headache
- dizziness
- impotence
- decreased energy or strength
- not feeling well
- pain

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of THALOMID. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

#### **How should I store THALOMID?**

- Store THALOMID at 77°F (25°C).
- Protect from light.

#### **Keep THALOMID and all medicines out of the reach of children.**

#### **General information about THALOMID**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Do not** take THALOMID for conditions for which it was not prescribed. **Do not** give THALOMID to other people, even if they have the same symptoms you have. It may harm them and may cause birth defects.

This Medication Guide provides a summary of the most important information about THALOMID. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about THALOMID that is written for healthcare professionals. You can also call 1-888-423-5436 or visit [www.THALOMID.com](http://www.THALOMID.com).

#### **What are the ingredients in THALOMID?**

Active ingredient: thalidomide

Inactive ingredients: pregelatinized starch and magnesium stearate.

The 50 mg capsule shell contains gelatin, titanium dioxide and black ink. The 100 mg capsule shell contains black iron oxide, yellow iron oxide, titanium dioxide, gelatin, and black ink. The 150 mg capsule shell contains FD&C blue #2, black iron oxide, yellow iron oxide, titanium dioxide, gelatin, and black and white ink. The 200 mg capsule shell contains FD&C blue #2, titanium dioxide, gelatin, and white ink.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured for Celgene Corporation

Summit, NJ 07901

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