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: EMBRYO-FETAL TOXICITY AND VENOUS THROMBOEMBOLISM

See full prescribing information for complete boxed warning.

EMBRYO -FETAL TOXICITY

- **If thalidomide is taken during pregnancy, it can cause severe birth defects or embryo-fetal death. Thalidomide should never be used by females 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 through a restricted distribution program, the THALOMID REMS™ program (formerly known as the System for Thalomid Education and Prescribing Safety (*S.T.E.P.S.*®) program) (5.2).

VENOUS THROMBOEMBOLISM

- **Significant increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with multiple myeloma receiving THALOMID® (thalidomide) with dexamethasone (5.3).**

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.3) 06/2014

----------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----------

- Ischemic heart disease (including myocardial infarction) and stroke have been observed in patients treated with THALOMID in combination with dexamethasone. (5.3)
- 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)

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

----------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 thromboembolism with THALOMID. (5.13, 7.4)
- Patients taking concomitant therapies such as erythropoietin stimulating agents or estrogen containing therapies may have an increased risk of thromboembolism. (7.7)

----------USE IN SPECIFIC POPULATIONS----------

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2014

*FULL PRESCRIBING INFORMATION: CONTENTS**

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY AND VENOUS THROMBOEMBOLISM

EMBRYO-FETAL TOXICITY

If thalidomide is taken during pregnancy, it can cause severe birth defects or embryo-fetal death. Thalidomide should never be used by females 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 embryo-fetal exposure to THALOMID® (thalidomide) as negligible as possible, THALOMID® (thalidomide) is approved for marketing only through a special restricted distribution program: THALOMID REMS™ program, approved by the Food and Drug Administration. This program was formerly known as the "System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*® program)".

You can get the information about THALOMID and the THALOMID REMS™ program on the Internet at www.celgeneriskmanagement.com or by calling the manufacturer's toll-free number 1-888-423-5436.

VENOUS THROMBOEMBOLISM

The use of THALOMID® (thalidomide) in multiple myeloma results in an increased risk of venous thromboembolism, 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 thromboembolism 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 THALOMID REMS™ PROGRAM. THALOMID® (THALIDOMIDE) MAY ONLY BE PRESCRIBED BY PRESCRIBERS CERTIFIED WITH THE THALOMID REMS™ PROGRAM AND MAY ONLY BE DISPENSED BY PHARMACISTS CERTIFIED WITH THE THALOMID REMS™ PROGRAM.

Drug prescribing to females of reproductive 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 THALOMID REMS™ 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 female *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)*. Thalidomide is contraindicated in females who are pregnant. 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.

4.2 Hypersensitivity

THALOMID is contraindicated in patients who have demonstrated hypersensitivity to the drug or its components *[see Warnings and Precautions (5.14)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

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, females of reproductive potential may be treated with thalidomide provided adequate precautions are taken to avoid pregnancy. THALOMID® (thalidomide) is only available through the THALOMID REMS™ program (formerly known as the "*S.T.E.P.S.*® program"), *[see Warnings and Precautions (5.2)]*.

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, females of reproductive potential should avoid contact with THALOMID® (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.

Females of Reproductive Potential
Females of reproductive potential must avoid pregnancy for at least 4 weeks before beginning THALOMID therapy, during therapy, during dose interruptions and for at least 4 weeks after completing therapy.

Females must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control, beginning 4 weeks prior to initiating treatment with THALOMID, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of THALOMID therapy.

Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing THALOMID therapy and then weekly during the first month, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles *[see Use in Specific Populations (8.6)]*.

Males
Thalidomide is present in the semen of patients receiving the drug. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking THALOMID and for up to 28 days after discontinuing THALOMID, even if they have undergone a successful vasectomy. Male patients taking THALOMID must not donate sperm *[see Use in Specific Populations (8.6)]*.

Blood Donation
Patients must not donate blood during treatment with THALOMID and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to THALOMID.

5.2 THALOMID REMS™ Program (*S.T.E.P.S.*®)

Because of the embryo-fetal risk *[see Warnings and Precautions (5.1)]*, THALOMID is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS), the **THALOMID REMS™** program (formerly known as the "*S.T.E.P.S.*®" program).

Required components of the **THALOMID REMS™** program include the following:

- Prescribers must be certified with the **THALOMID REMS™** program by enrolling and complying with the REMS requirements.
- Patients must sign a Patient-Physician Agreement Form and comply with the REMS requirements. In particular, female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.6)]* and males must comply with contraception requirements *[see Use in Specific Populations (8.6)]*.

- Pharmacies must be certified with the **THALOMID REMS™** program, must only dispense to patients who are authorized to receive THALOMID and comply with REMS requirements.

Further information about the **THALOMID REMS™** program is available at www.celgeneriskmanagement.com or by telephone at 1-888-423-5436.

5.3 Venous and Arterial Thromboembolism

The use of THALOMID in patients with MM results in an increased risk of venous thromboembolism, 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 thromboembolism was 22.5% in patients receiving thalidomide in combination with dexamethasone compared to 4.9% in patients receiving dexamethasone alone ($p = 0.002$).

Ischemic heart disease (11.1%), including myocardial infarction (1.3%), and stroke (cerebrovascular accident, 2.6%) have also occurred in patients with previously untreated MM treated with THALOMID and dexamethasone compared to placebo and dexamethasone (4.7%, 1.7%, and 0.9%, respectively) in one clinical trial *[see Adverse Reactions (6.1)]*.

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. Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling *[see Boxed Warning]*. Agents that also may increase the risk of thromboembolism should be used with caution in patients receiving THALOMID *[see Drug Interactions (7.7)]*.

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 (≥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 $<750/mm^3$. 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 $750/mm^3$ 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

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.