CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-785

Approved Labeling

WARNING: SEVERE, LIFE-THREATENING HUMAN BIRTH DEFECTS

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 (50 mg)] 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 AS NEGLIGIBLE AS POSSIBLE, THALOMID 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.)".

UNDER THIS RESTRICTED DISTRIBUTION PROGRAM, ONLY PRESCRIBERS AND PHARMACISTS REGISTERED WITH THE PROGRAM ARE ALLOWED TO PRESCRIBE AND DISPENSE THE PRODUCT. IN ADDITION, PATIENTS MUST BE ADVISED OF, AGREE TO, AND COMPLY WITH THE REQUIREMENTS OF THE S.T.E.P.S. PROGRAM IN ORDER TO RECEIVE PRODUCT.

PLEASE SEE THE FOLLOWING BOXED WARNINGS CONTAINING SPECIAL INFORMATION FOR PRESCRIBERS, FEMALE PATIENTS, AND MALE PATIENTS ABOUT THIS RESTRICTED DISTRIBUTION PROGRAM.

PRESCRIBERS

THALOMID™ (thalidomide) may be prescribed only by licensed prescribers who are registered in the *S.T.E.P.S.* 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, micro pinna, 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.[1] Mortality at or shortly after birth has been reported at about 40%.[2]

Effective contraception (see **CONTRAINDICATIONS**) must be used for at least 1 month before beginning thalidomide therapy, during thalidomide therapy, and for 1 month following discontinuation of thalidomide therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or because the patient has been post-menopausal for at least 24 months. Two reliable forms of contraception must be used simultaneously unless continuous abstinence from reproductive heterosexual sexual intercourse is the chosen method. 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 post-menopausal 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 child-bearing 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 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.

Once treatment has started, pregnancy testing should occur weekly during the first month of use, then monthly thereafter 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 (thalidomide) must be reported immediately to the FDA *via* the MedWATCH number at 1-800-FDA-1088 and also to Celgene Corporation. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

FEMALE PATIENTS

Thalidomide 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.*) 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 (see **CONTRAINDICATIONS**), unless continuous abstinence from reproductive heterosexual intercourse is the chosen method. (Sexually mature women who have not undergone a hysterectomy or who have not been post-menopausal 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 child-bearing potential.).
- she acknowledges, in writing, her understanding of these warnings and of the need for using two reliable methods of contraception for one month prior to starting thalidomide therapy, during thalidomide therapy, and for one month after stopping 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. (See **PRECAUTIONS, CONTRAINDICATIONS.**)
- 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

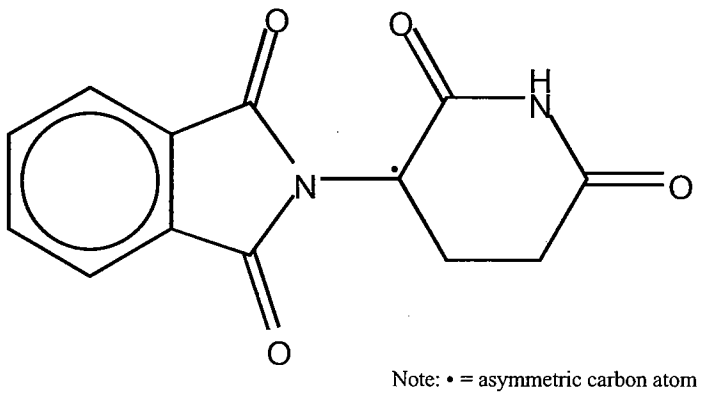
Thalidomide is contraindicated in sexually mature MALES unless the PATIENT MEETS ALL OF THE FOLLOWING CONDITIONS:

- 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.* 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 need to use barrier contraception when having sexual intercourse with women of childbearing potential, even if he has undergone successful vasectomy.
- he acknowledges, in writing, his understanding of these warnings and of the need for using barrier contraception (latex condom), even if he has undergone successful vasectomy, when having sexual intercourse with women of childbearing potential. Sexually mature women who have not undergone a hysterectomy or who have not been post-menopausal 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 child-bearing 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.

DESCRIPTION

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

THALOMID (thalidomide) is available in 50 mg capsules for oral administration. Active ingredient: thalidomide. Inactive ingredients: anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

CLINICAL PHARMACOLOGY

Mechanism of Action

Thalidomide is an immunomodulatory agent with a spectrum of activity that is not fully characterized. In patients with erythema nodosum leprosum (ENL) the mechanism of action is not fully understood.

Available data from *in vitro* studies and preliminary clinical trials suggest that the immunologic effects of this compound can vary substantially under different conditions, but, may be related to suppression of excessive tumor necrosis factor-alpha (TNF-α) production and down-modulation of selected cell surface adhesion molecules involved in leukocyte migration[3,4,5,6]. For example, administration of thalidomide has been reported to decrease circulating levels of TNF-α in patients with ENL[3], however, it has also been shown to increase plasma TNF-α levels in HIV-seropositive patients[7].

Pharmacokinetics and Drug Metabolism

Absorption

The absolute bioavailability of thalidomide from THALOMID capsules has not yet been characterized in human subjects due to its poor aqueous solubility. In studies of both healthy volunteers and subjects with Hansen's disease, the mean time to peak plasma concentrations (T_{max}) of THALOMID ranged from 2.9 to 5.7 hours indicating that THALOMID is slowly absorbed from the gastrointestinal tract. While the extent of absorption (as measured by area

under the curve [AUC]) is proportional to dose in healthy subjects, the observed peak concentration (C_{max}) increased in a less than proportional manner (see Table 1 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 1
Pharmacokinetic Parameter Values for THALOMID (thalidomide)
Mean (%CV)

Population/ Single Dose	AUC_{0-} (µg hr/mL)	C_{max} (µg/mL)	T_{max} (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%)

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

Distribution

It is not known whether thalidomide is present in the ejaculate of males.
The extent of plasma protein binding of thalidomide is unknown.

Metabolism

At the present time, the exact metabolic route and fate of thalidomide is not known in humans. Thalidomide itself does not appear to be hepatically metabolized to any large extent, but appears to undergo non-enzymatic hydrolysis in plasma to multiple metabolites. In a repeat dose study in which THALOMID (thalidomide) 200 mg was administered to 10 healthy females for 18 days, thalidomide displayed similar pharmacokinetic profiles on the first and last day of dosing. This suggests that thalidomide does not induce or inhibit its own metabolism.

Elimination

As indicated in Table 1 (above) the mean half-life of elimination ranges from approximately 5 to 7 hours following a single dose and is not altered upon multiple dosing. As noted in the metabolism subsection, the precise metabolic fate and route of elimination of thalidomide in humans is not known at this time. Thalidomide itself has a renal clearance of 1.15 mL/minute with less than 0.7% of the dose excreted in the urine as unchanged drug. Following a single dose, urinary levels of thalidomide were undetectable 48 hrs after dosing. Although thalidomide is thought to be hydrolyzed to a number of metabolites[8], only a very small amount (0.02% of the administered dose) of 4-OH-thalidomide was identified in the urine of subjects 12 to 24 hours after dosing.

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 (thalidomide) 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.

Patients with Renal Insufficiency: The pharmacokinetics of thalidomide in patients with renal dysfunction have not been determined.

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

Age: 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.

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

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

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

Clinical Studies

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 2
Double Blind, Controlled Clinical Trials of Thalidomide in Patients with ENL: Cutaneous Response

Reference	No. of Patients	No. Treatment Courses*	Percent Responding**	
Iyer *et al.*[9] Bull World Health Organization 1971; 45:719	92	204	Thalidomide 75%	Aspirin 25%
Sheskin *et al.*[10] Int J Lep 1969; 37:135	52	173	Thalidomide 66%	Placebo 10%

* In patients with cutaneous lesions
** Iyer: Complete response or lesions absent

** Sheskin: Complete Improvement + "striking" improvement (i.e., >50% improvement)

Waters[11] 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 3
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[11]	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 reinstitution of therapy.

Twenty U.S. patients between the ages of 11 and 17 years were treated wtih 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.

INDICATIONS AND USAGE

THALOMID (thalidomide) is indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL). THALOMID (thalidomide) is not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis.

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

CONTRAINDICATIONS (See BOXED WARNINGS.)

Pregnancy: Category X

Due to its known human teratogenicity, even following a single dose, thalidomide is contraindicated in pregnant women and women capable of becoming pregnant. (See **BOXED WARNINGS.**) When there is no alternative treatment, women of childbearing potential may be treated with thalidomide provided adequate precautions are taken to avoid pregnancy. Women

must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control, including at least one highly effective method (*e.g.*, IUD, hormonal contraception, tubal ligation, or partner's vasectomy) and one additional effective method (*e.g.*, latex condom, diaphragm, or cervical cap), beginning 4 weeks prior to initiating treatment with thalidomide, during therapy with thalidomide, and continuing for 4 weeks following discontinuation of thalidomide therapy. If hormonal or IUD contraception is medically contraindicated (see also **PRECAUTIONS: DRUG INTERACTIONS**), two other effective or highly effective methods may be used.

Women of childbearing potential being treated with thalidomide should have pregnancy testing (sensitivity of at least 50 mIU/mL). The test should be performed within the 24 hours before beginning thalidomide therapy and then weekly during the first month of thalidomide therapy, then monthly thereafter 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. If pregnancy occurs during thalidomide treatment, thalidomide must be immediately discontinued. Under these conditions, the patient should be referred to an obstetrician / gynecologist experienced in reproductive toxicity for further evaluation and counseling.

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

WARNINGS (See BOXED WARNINGS.)

Birth defects:

Thalidomide can cause severe birth defects in humans. (See **BOXED WARNING** and **CONTRAINDICATIONS.**) Patients should be instructed to take thalidomide only as prescribed and not to share their thalidomide with anyone else. Because it is not known whether or not thalidomide is present in the ejaculate of males receiving the drug, males receiving thalidomide must always use a latex condom when engaging in sexual activity with women of childbearing potential.

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. Patients should be advised as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks, such as driving a car or operating other complex or dangerous machinery.

Peripheral neuropathy:

Thalidomide is known to cause nerve damage that may be permanent. Peripheral neuropathy is a common, potentially severe, side effect of treatment with thalidomide that may be irreversible. Peripheral neuropathy generally occurs following chronic use over a period of months, however, reports following relatively short term use also exist. The correlation with cumulative dose is

unclear. Symptoms may occur some time after 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.

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.

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 on-going 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.

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)[7]. A similar trend was observed in a second, unpublished study conducted in patients who were HIV-seropostive[12]. 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.

PRECAUTIONS

Hypersensitivity:

Hypersensitivity to THALOMID (thalidomide) 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 (thalidomide) should be discontinued.

Bradycardia:

Bradycardia in association with thalidomide use has been reported. At present there have been no reports of bradycardia requiring medical or other intervention. The clinical significance and underlying etiology of the bradycardia noted in some thalidomide-treated patients are present unknown.

Information for Patients (See BOXED WARNINGS.)

Patient should be instructed about the potential teratogenicity of thalidomide and the precautions that must be taken to preclude fetal exposure as per the S.T.E.P.S. program and boxed warnings in this package insert. Patients should be instructed to take thalidomide only as prescribed in compliance with all of the provisions of the S.T.E.P.S. Restricted Distribution Program.

Patients should be instructed not to share medication with anyone else.

Patients should be instructed that 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. Patients should be advised as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks, such as driving a car or operating other complex machinery. Patients should be instructed that thalidomide may potentiate the somnolence caused by alcohol.

Patients should be instructed that thalidomide can cause peripheral neuropathies that may be initially signaled by numbness, tingling, or pain or a burning sensation in the feet or hands. Patients should be instructed to report such occurrences to their prescriber immediately.

Patients should also be instructed 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.

Patients should be instructed that they are not permitted to donate blood while taking thalidomide. In addition, male patients should be instructed that they are not permitted to donate sperm while taking thalidomide.

Laboratory Tests

Pregnancy Testing: **(See BOXED WARNINGS.)** Women of childbearing potential should have

pregnancy testing performed (sensitivity of at least 50 mIU/mL). The test should be performed within the 24 hours prior to beginning thalidomide therapy and then weekly during the first month of use, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Pregnancy testing should also be performed if a patient misses her period or if there is any abnormality in menstrual bleeding.

Neutropenia: **(See WARNINGS.)**

HIV Viral Load: **(See WARNINGS.)**

Drug Interactions

Thalidomide has been reported to enhance the sedative activity of barbiturates, alcohol, chlorpromazine, and reserpine.

Peripheral Neuropathy: Medications known to be associated with peripheral neuropathy should be used with caution in patients receiving thalidomide.

Oral Contraceptives: In 10 healthy women, the pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of a single dose containing 1.0 mg of norethindrone acetate and 75 μg of ethinyl estradiol were studied. The results were similar with and without coadministration of thalidomide 200 mg/day to steady-state levels.

Important Non-Thalidomide Drug Interactions

Drugs That Interfere with Hormonal Contraceptives: Concomitant use of HIV-protease inhibitors, griseofulvin, rifampin, rifabutin, phenytoin, or carbamazepine with hormonal contraceptive agents, may reduce the effectiveness of the contraception. Therefore, women requiring treatment with one or more of these drugs must use two OTHER effective or highly effective methods of contraception or abstain from reproductive heterosexual sexual intercourse.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity tests have not been conducted using thalidomide. Thalidomide gave no evidence of mutagenic effects when assayed in *in vitro* bacterial (*Salmonella typhimurium* and *Escherichia coli*; Ames mutagenicity test), *in vitro* mammalian (AS52 Chinese hamster ovary cells; AS52/XPRT mammalian cell forward gene mutation assay) and *in vivo* mammalian (CD-1 mice; *in vivo* micronucleus test) test systems.

Animal studies to characterize the effects of thalidomide on fertility have not been conducted.

Pregnancy

Pregnancy Category X: **See BOXED WARNING and CONTRAINDICATIONS.**

Because of the known human teratogenicity of thalidomide, thalidomide is contraindicated in women who are or may become pregnant and who are not using the two required types of birth

control or who are not continually abstaining from reproductive heterosexual sexual intercourse. 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 (50 mg)] taken by a pregnant woman can cause birth defects. 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 counselling. Any suspected fetal exposure to THALOMID (thalidomide) must be reported to the FDA *via* the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation.

Animal studies to characterize the effects of thalidomide on late stage pregnancy have not been conducted.

Use in Nursing Mothers

It is not known whether thalidomide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from thalidomide, 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.

Pediatric Use

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

Geriatric Use

No systematic studies in geriatric patients have been conducted. Thalidomide has been used in clinical trials in patients up to 90 years of age. Adverse events in patients over the age of 65 years did not appear to differ in kind from those reported for younger individuals.

ADVERSE REACTIONS

The most serious toxicity associated with thalidomide is its documented human teratogenicity. (See **BOXED WARNINGS** and **CONTRAINDICATIONS**) 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.

Thalidomide is associated with drowsiness / somnolence, peripheral neuropathy, dizziness / orthostatic hypotension, neutropenia, and HIV viral load increase. **(See WARNINGS.)**

Hypersensitivity to THALOMID (thalidomide) and bradycardia in patients treated with thalidomide have been reported. **(See PRECAUTIONS.)**

Somnolence, dizziness, and rash are the most commonly observed adverse events associated with the use of thalidomide. Thalidomide has been studied in controlled and uncontrolled clinical trials

in patients with ENL and in people who are HIV-seropositive. In addition, thalidomide has been administered investigationally for more than 20 years in numerous indications. Adverse event profiles from these uses are summarized in the sections that follow.

Other Adverse Events:

Due to the nature of the longitudinal data that form the basis of this product's safety evaluation, no determination has been made of the causal relationship between the reported adverse events listed below and thalidomide. These lists are of various adverse events noted by investigators in patients to whom they had administered thalidomide under various conditions.

Incidence in Controlled Clinical Trials

Table 4 lists treatment-emergent signs and symptoms that occurred in THALOMID-treated patients in controlled clinical trials in ENL. Doses ranged from 50 to 300 mg/day. All adverse events were mild to moderate in severity, and none resulted in discontinuation. Table 4 also lists treatment-emergent adverse events that occurred in at least 3 of the THALOMID-treated HIV-seropositive patients who participated in an 8-week, placebo controlled clinical trial. Events that were more frequent in the placebo-treated group are not included. (See **WARNINGS, PRECAUTIONS,** and **DRUG INTERACTIONS.**)

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

Body System/Adverse Event	All AEs Reported in ENL Patients	AEs Reported in HIV-seropositive Patients		
		Thalidomide		Placebo
	50 to 300 mg/day (N=24)	100 mg/day (N=36)	200 mg/day (N=32)	(N=35)
Body as a Whole	**16 (66.7%)**	**18 (50.0%)**	**19 (59.4%)**	**13 (37.1%)**
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%)
Digestive System	**5 (20.8%)**	**16 (44.4%)**	**16 (50.0%)**	**15 (42.9%)**
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
Hemic and Lymphatic	**0**	**8 (22.2%)**	**13 (40.6%)**	**10 (28.6%)**
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%)
Metabolic and Endocrine Disorders	**1 (4.2%)**	**8 (22.2%)**	**12 (37.5%)**	**8 (22.9%)**
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%)
Nervous System	**13 (54.2%)**	**19 (52.8%)**	**18 (56.3%)**	**12 (34.3%)**
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
Respiratory System	**3 (12.5%)**	**9 (25.0%)**	**6 (18.7%)**	**9 (25.7%)**
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%)
Skin and Appendages	**10 (41.7%)**	**17 (47.2%)**	**18 (56.3%)**	**19 (54.3%)**
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 maculo-papular	1 (4.2%)	6 (16.7%)	6 (18.7%)	2 (5.7%)
Sweating	0	0	4 (12.5%)	4 (11.4%)
Urogenital System	**2 (8.3%)**	**6 (16.7%)**	**2 (6.3%)**	**4 (11.4%)**
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

Thalidomide in doses up to 400 mg/day has been administered investigationally 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. As mentioned previously, **no causal relationship between thalidomide 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.

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, alkaline phosphatase, 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, vasodilation.

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, that are too general to be informative.

Body as a Whole: Ascites, AIDS, allergic reaction, cellulitis, chest pain, chills and fever, cyst, decreased CD4 count, facial edema, flu syndrome, hernia, 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, hyperlipemia, 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.

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, and suicide attempt.

DRUG ABUSE AND DEPENDENCE

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

OVERDOSAGE

There have been three cases of overdose reported, all attempted suicides. There have been no reported fatalities in doses of up to 14.4 grams, and all patients recovered without reported sequelae.

DOSAGE AND ADMINISTRATION

THALOMID MUST ONLY BE ADMINISTERED IN COMPLIANCE WITH ALL OF THE TERMS OUTLINED IN THE S.T.E.P.S. PROGRAM. THALOMID 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.

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.

HOW SUPPLIED

(THIS PRODUCT IS ONLY SUPPLIED TO PHARMACISTS REGISTERED WITH THE S.T.E.P.S. PROGRAM - See BOXED WARNINGS.)

THALOMID (thalidomide) is supplied in hard gelatin, 50 mg capsules [white opaque], imprinted "Celgene" with a "do not get pregnant" logo. Boxes containing six prescription packs of 14 capsules each (84 capsules total).

NDC Number(s)
59572-105-02

STORAGE AND DISPENSING

PHARMACISTS NOTE:

DRUG MUST ONLY BE DISPENSED IN NO MORE THAN A 1-MONTH SUPPLY AND ONLY ON PRESENTATION OF A NEW PRESCRIPTION WRITTEN WITHIN THE PREVIOUS 14 DAYS. SPECIFIC INFORMED CONSENT (copy attached as part of this package insert) AND COMPLIANCE WITH THE MANDATORY PATIENT REGISTRY AND SURVEY ARE REQUIRED FOR ALL PATIENTS (MALE AND FEMALE) PRIOR TO DISPENSING BY THE PHARMACIST.

This drug must not be repackaged.

Store at 59 to 86°F; 15 to 30°C. Protect from light.

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

Manufactured by Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059

Important Information and Warnings For All Patients Taking THALOMID™ (thalidomide)

WARNING: SERIOUS HUMAN BIRTH DEFECTS

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 (50 mg)] TAKEN BY A PREGNANT WOMAN CAN CAUSE SEVERE BIRTH DEFECTS.

CONSENT FOR WOMEN:

INIT:___ 1. I understand that I must not take THALOMID™ (thalidomide) if I am pregnant, breast-feeding a baby, or able to get pregnant and not using the required two methods of birth control.

INIT:___ 2. I understand that severe birth defects can occur with the use of THALOMID™ (thalidomide). I have been warned by my doctor that my unborn baby will almost certainly have serious birth defects or may even die if I am pregnant or become pregnant while taking THALOMID™ (thalidomide).

INIT:___ 3. I understand that if I am able to become pregnant, I must use at least one highly effective method and one additional effective method of birth control (contraception) AT THE SAME TIME:

At least one highly effective method		**One additional effective method**
IUD	**AND**	Latex condom
Hormonal (Birth control pills)		Diaphragm
Tubal ligation		Cervical cap
Partner's vasectomy		

These birth control methods must be used for at least 4 weeks before starting THALOMID therapy, all during THALOMID therapy, and for at least 4 weeks after THALOMID therapy has stopped. I must use these methods even if I am infertile, unless I have has a hysterectomy or because I have been post-menopausal for at least 24 months (been through the changes of life). The only exception is if I completely avoid heterosexual sexual intercourse. If a hormonal (birth control pills) or IUD method is not medically possible for me, I may use another highly effective method or two barrier methods AT THE SAME TIME.

INIT:___ 4. I know that I must have a pregnancy test done by my doctor within the 24 hours prior to starting THALOMID therapy, then every week during the first 4 weeks of THALOMID therapy. I will then have a pregnancy test every 4 weeks if I have regular menstrual cycles, or every 2 weeks if my cycles are irregular while I am taking THALOMID.

INIT:___ 5. I know that I must immediately stop taking THALOMID™ and inform my doctor if I become pregnant while taking the drug; if I miss my menstrual period, or experience unusual menstrual bleeding; stop using birth control; or think, FOR ANY REASON, that I may be pregnant. If my doctor is not available, I can call 1-888-668-2528 for information on emergency contraception.

INIT:___ 6. I am not now pregnant, nor will I try to become pregnant for at least 4 weeks after I have completely finished taking THALOMID™.

INIT:___ 7. I understand that THALOMID™ will be prescribed ONLY for me. I must NOT share it with ANYONE, even someone who has symptoms similar to mine. It must be kept out of the reach of children and should never be given to women who are able to have children.

INIT:___ 8. I have read the THALOMID™ patient brochure and/or viewed the videotape, "Important Information for Men and Women Taking THALOMID™ (thalidomide)". I understand the contents, including other possible health problems from THALOMID™, so-called "side effects". I know that I cannot donate blood while taking THALOMID™.

INIT:___ 9. My doctor has answered any questions I have asked.

INIT:___ 10. I understand that I must participate in a survey and patient registry while I am on THALOMID™, which will require completing additional forms.

CONSENT FOR MEN:

INIT:___ 1. I understand that I must not take THALOMID™ if I cannot avoid unprotected sex with a woman , even if I have had a successful vasectomy.

INIT:___ 2. I understand that severe birth defects or death to an unborn baby have occurred when women took thalidomide during pregnancy.

INIT:___ 3. I have been told by my doctor that I must NEVER have unprotected sex with a woman because it is not known if the drug is present in semen or sperm. My doctor has explained that I must either completely avoid heterosexual sexual intercourse or I must use a latex condom EVERY TIME I have sexual intercourse with a female partner while I am taking THALOMID™ - and for 4 weeks after I stop taking the drug, even if I have had a successful vasectomy.

INIT:___ 4. I also know that I must inform my doctor if I have had unprotected sex with a woman; or if I think, FOR ANY REASON, that my sexual partner may be pregnant. If my doctor is not available, I can call 1-888-668-2528 for information on emergency contraception.

INIT:___ 5. I understand that THALOMID™ will be prescribed ONLY for me. I must NOT share it with ANYONE, even someone who has symptoms similar to mine. It must be kept out of the reach of children and should never be given to women who are able to have children.

INIT:___ 6. I have read the THALOMID™ patient brochure and/or viewed the videotape, "Important Information for Men and Women Taking THALOMID™ (thalidomide)". I understand the contents, including other possible health problems from THALOMID™ (thalidomide), so-called "side effects". I know that I cannot donate blood or semen while taking THALOMID™ (thalidomide).

INIT:___ 7. My doctor has answered any questions I have asked.

INIT:___ 8. I understand that I must participate in a survey and patient registry while I am on THALOMID™, which will require completing additional forms.

Authorization:

This information has been read aloud to me in the language of my choice. I understand that if I do not follow all of my doctor's instructions, I will not be able to receive THALOMID™ . I now authorize my doctor to begin my treatment with THALOMID™ .

Patient Name (please print)	Social Security No. (Only last six digits required)	Date of Birth (mo./day/yr.)

Patient, Parent / Guardian Signature Date (mo./day/yr.)

I have fully explained to the patient the nature, purpose, and risks of the treatment described above, especially the risks to women of childbearing potential. I have asked the patient if she/he has any questions regarding her/his treatment with THALOMID™ and have answered those questions to the best of my ability. I will ensure that the appropriate components of the patient consent form are completed. In addition, I will comply with all of my obligations and responsibilities as a prescriber registered under the S.T.E.P.S. restricted distribution program.

Physician Name (please print) DEA No.

Physician Signature Date (mo./day/yr.)

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