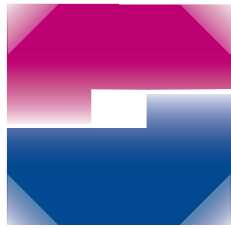


System for
Thalidomide
Education and
Prescribing
Safety



THALOMID™
(thalidomide)

Balancing the Benefits and the Risks



Foreword

The introduction of thalidomide in the 1950s as a treatment for insomnia and morning sickness was responsible for the occurrence of more than 10,000 reported cases of birth defects. Birth defects following thalidomide exposure during pregnancy include missing or abnormal legs, arms, feet, and hands; spinal cord defects; cleft lip or palate; absent or abnormal external ears; heart, kidney, and genital abnormalities; and abnormal formation of the digestive system.

Thalidomide continues to be used as a clinical research tool and is currently in Phase II/III trials for a number of therapeutic indications. The drug is now commercially available in the United States 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. (Concurrent use of steroids is indicated in the presence of neuritis.) It is important for health-care professionals to remember that the serious risk of birth defects related to thalidomide remains essentially the same today as when the product was originally marketed. However, today the risks are known and can therefore be minimized. Additional adverse effects and risks have been identified in various patient populations.

The teratogenic potential of thalidomide is well known. Other commonly observed adverse events associated with thalidomide use include drowsiness/somnolence, peripheral neuropathy, dizziness and orthostatic hypotension, neutropenia, increased HIV-viral load, hypersensitivity (including the occurrence of rash, possibly associated with fever, tachycardia, and hypotension), and bradycardia. If this drug is to be used to benefit individuals with a severe, debilitating disease such as ENL, prescribers, pharmacists, and patients must be fully aware of the dangers of fetal exposure and use the drug according to mandatory guidelines. The promise of the agent must be balanced with the known toxicity and the accompanying ethical and legal constraints on its use.

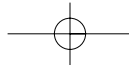


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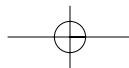
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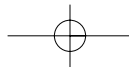
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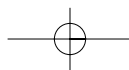
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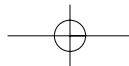
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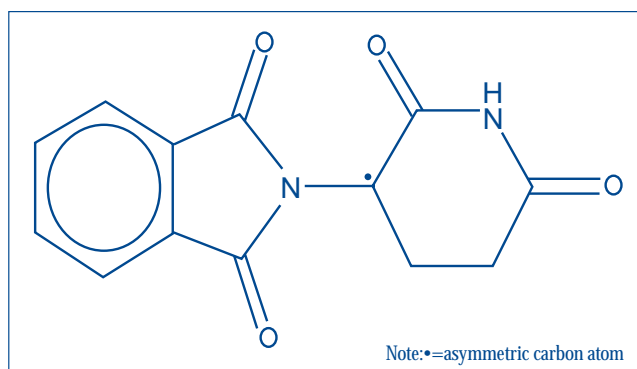




CHEMISTRY

Thalidomide is an immunomodulatory agent with the chemical name of α -(N-phthalimido)glutarimide.¹ The empiric formula for thalidomide is $C_{13}H_{10}N_2O_4$; it has a gram molecular weight of 258.2.¹

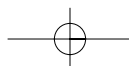
Figure 1. Chemical structure of thalidomide.¹



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.¹

The chemical structure of thalidomide is shown in Figure 1.¹ The glutarimide moiety contains a single asymmetric center, and therefore may exist in either of two optically active forms, designated S-(-) or R-(+).^{1,2} THALOMID™ (thalidomide) is an equal mixture of the S-(-) and R-(+) forms, and therefore has a net optical rotation of zero.¹ In vitro incubation of thalidomide in blood confirms that the enantiomers rapidly interconvert in biologic media at physiologic pH.^{3,4,5,6,7,8}

Each THALOMID™ (thalidomide) capsule contains 50 mg of thalidomide with anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin as inactive ingredients.¹



CLINICAL PHARMACOLOGY

Pharmacology and Mechanism of Action: Overview

THALOMID™ (thalidomide) is an immunomodulatory agent with a spectrum of activity that is not fully characterized.¹ In patients with ENL, the mechanism of action is not fully understood.¹

Available data from in vitro studies and preliminary clinical trials suggest that the immunologic effects of thalidomide can vary substantially under different conditions, but may be related to suppression of excessive tumor necrosis factor- α (TNF- α) production and downmodulation of selected cell surface adhesion molecules involved in leukocyte migration.^{1,7,10,11} For example, administration of the drug has been reported to decrease circulating levels of TNF- α in patients with ENL,¹¹ but has also been shown to increase plasma TNF- α levels in HIV-seropositive patients.^{1,12}

Tumor Necrosis Factor- α Inhibition

Thalidomide decreases TNF- α production by accelerating the degradation of mRNA encoding the protein.^{1,13-15} This mechanism differs from the mechanism of action proposed for pentoxifylline and corticosteroids, which suppress lipopolysaccharide (LPS)-induced TNF- α RNA transcription and translation, respectively.^{1,14}

In vitro, thalidomide selectively inhibited human monocyte TNF- α production stimulated by LPS or mycobacterium-based agonists.^{1,7} The inhibition was concentration-dependent and occurred at concentrations comparable to serum levels achieved in vivo with thalidomide doses up to 400 mg/d.^{1,7} The level of TNF- α inhibition in vitro was about 40% at the clinically achievable serum concentration of 1 μ g/mL.^{1,7}

Abnormally high serum levels of TNF- α and interferon gamma (IFN- γ) are measurable in the serum of patients with ENL.^{1,11,13,16-18} Thalidomide 100 to 300 mg/d has been shown to reduce these levels to baseline in some ENL patients, coincident with alleviation of symptoms (Figure 2).^{1,11,17} Thalidomide treatment also is associated with a similar decrease in agonist-stimulated monocyte TNF- α secretion in vitro.^{1,13,18} Thalidomide treatment also decreased dermal infiltration of polymorphonuclear leukocytes and T cells and downregulated expression of surface adhesion molecules and major histocompatibility antigens on the endothelium and epidermal keratinocytes.¹¹

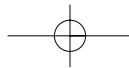
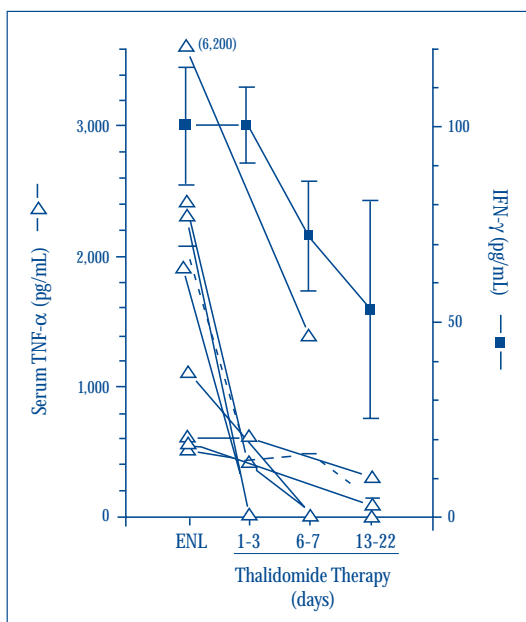
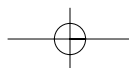


Figure 2. Effect of thalidomide treatment on serum TNF- α and IFN- γ levels in 8 ENL patients tested at onset of reactional episode and during treatment with thalidomide. TNF- α levels (pg/mL) are shown for each patient. Mean is shown by dashed line. IFN- γ levels (pg/mL) are means \pm SE. Cytokine levels are expressed as pg/mL. Reprinted with permission from Sampaio et al.¹¹



In vitro in LPS-stimulated alveolar macrophages obtained from 31 patients with tuberculosis or other diseases associated with macrophage activation, thalidomide caused a significant ($P < 0.05$) reduction in the LPS-induced increase in the number of cells staining with antibodies to TNF- α .¹⁹ Thalidomide also significantly ($P < 0.05$) reduced TNF- α mRNA expression compared with that observed in cells incubated with medium alone.¹⁹ In patients coinfecting with human immunodeficiency virus-1 (HIV-1) and *Mycobacterium tuberculosis* who were receiving antituberculosis treatment, thalidomide treatment caused a $\geq 10\%$ reduction in plasma TNF- α levels ($P = 0.06$ for the change during treatment, Wilcoxon signed-rank test).²⁰ The reduction was most pronounced in patients who had increased TNF- α levels prior to thalidomide treatment.²⁰ In comparison, patients receiving anti-tuberculosis therapy and placebo did not show a significant reduction in TNF- α levels.²⁰



Immunomodulatory Effects

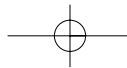
Some in vitro and in vivo observations in patients with ENL have suggested that this inflammatory reaction results from transient activation of the cell-mediated immune (CMI) cascade, which may be altered by thalidomide.^{1,21,22} In healthy male volunteers, thalidomide 200 mg/d for 4 days induced a significant ($P < 0.001$) decrease in the circulating helper T-cell to suppressor T-cell ratio (H:S ratio) compared with pretreatment and 2-week posttreatment values.²³ The decreased H:S ratio resulted from a significant ($P < 0.01$) decrease in the percentage and absolute numbers of circulating helper T cells and an apparent increase ($P < 0.05$) in the percentage and absolute numbers of suppressor T cells.²³ In vivo, thalidomide modifies a number of integrin receptors, including $\beta 1$ -integrins, $\beta 2$ -integrins, and surface components such as the “homing receptor” (CD44) and other surface receptors such as ICAM-1 and selectins.¹⁰ CD45R0 receptor densities on CD4 helper cells are greatly reduced,¹⁰ and thalidomide also strongly downregulates CD11a, CD11b, and CD18 on leukocytes.¹⁰ These effects are very pronounced, apparently dose-dependent, and completely reversible.¹⁰ In vitro, thalidomide significantly reduces HIV-1 replication in peripheral blood mononuclear cells (PBMCs) from HIV-1-infected hosts and in agonist-stimulated latently infected cell lines.¹⁵ Thalidomide inhibition of viral activation in infected PBMCs may be expressed through the monocyte population, although this has not been conclusively demonstrated.¹⁵

Central Nervous System Effects

The sedative-hypnotic properties of thalidomide are most likely mediated by its glutarimide ring, which is the configuration for several other sedative-hypnotic drugs.³ In vivo, thalidomide has been shown to be a sedative-hypnotic drug acting differently from barbiturates, possibly involving activation of a forebrain sleep center.^{3,8} Thalidomide causes a marked reduction in motor activity, inducing sleep in mice at oral doses of 100 mg.⁸ However, it does not cause incoordination, respiratory depression, or narcosis.^{3,8} In addition, it is devoid of anticonvulsant, analgesic, and hypothermic activity, and has only slight antipyretic activity in mice.⁸

Antiangiogenic Effects

In animal models, thalidomide 200 mg/kg inhibited vascularization induced by basic fibroblast growth factor (bFGF) in the rabbit corneal micropocket model by 30% to 50% (median inhibition = 36%; $P = 0.0001$, two-way ANOVA with ranked data).²⁴ This inhibition of angiogenesis was observed after only two doses.²⁴ The mechanism by which thalidomide inhibits angiogenesis is unknown.²⁴ The drug has no effect on bFGF-induced proliferation of endothelial cells in culture.²⁴ Current studies are focused on identifying possible active thalidomide metabolites, since the effect of thalidomide on growing vessels is observed only when the drug is administered orally (suggesting the need for formation of an active metabolite in vivo).²⁴



Clinical Pharmacokinetics

Absorption

The absolute bioavailability of thalidomide from THALOMID™ (thalidomide) capsules has not yet been characterized in humans due to its poor aqueous solubility.¹ In studies of both healthy volunteers and subjects with Hansen's disease, the mean time to peak plasma concentrations (T_{max}) of THALOMID™ (thalidomide) ranged from 2.9 to 5.7 hours, indicating that THALOMID™ (thalidomide) is slowly absorbed from the gastrointestinal tract.¹ While the extent of absorption (as measured by the area under the plasma concentration-time curve [AUC]) is proportional to dose in healthy subjects, the observed peak concentration (C_{max}) increased in a less than proportional manner (Table 1).¹ 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.¹ Coadministration of thalidomide with a high-fat meal causes minor (<10%) changes in the observed AUC and C_{max} values, but causes an increase in T_{max} to approximately 6 hours.¹

Table 1. Pharmacokinetic parameter values (mean [% CV]) for THALOMID™ (thalidomide) following single doses¹

THALOMID™ (thalidomide) Dose	AUC _{0-∞} (μg•h/mL)	C _{max} (μg/mL)	T _{max} (hours)	Half-life (hours)
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%)	3.44 (52.6%)	5.7 (27%)	6.86 (17%)

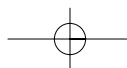
CV=covariance; AUC=area under the plasma concentration-time curve; C_{max}=maximum plasma concentration;
T_{max}=time to maximum plasma concentration.

Distribution

It is not known whether thalidomide is present in the ejaculate of males.¹ The extent of plasma protein binding of thalidomide is unknown.¹

Metabolism

At the present time, the exact metabolic route and fate of thalidomide in humans are not known.¹ Thalidomide itself does not appear to be hepatically metabolized to any large extent, but appears to undergo nonenzymatic hydrolysis in plasma to multiple metabolites.¹ 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.¹ This suggests that thalidomide does not induce or inhibit its own metabolism.¹



Elimination

The mean elimination half-life of thalidomide is approximately 5 to 7 hours following a single dose and is not altered after multiple dosing.¹ As previously noted, the precise metabolic fate and route of elimination of thalidomide in humans are not currently known.¹ Renal clearance of thalidomide itself is 1.15 mL/min,¹ indicating mainly nonrenal elimination. Urinary excretion of thalidomide was small, with 0.7% of the dose excreted unchanged in urine.¹ Following a single dose, urinary levels of thalidomide were undetectable 48 hours after dosing.¹ Although thalidomide is thought to be hydrolyzed to a number of metabolites, 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.¹

Special Populations

HIV-Seropositive Patients

There is no apparent significant difference in measured pharmacokinetic parameter values between healthy human volunteers and HIV-seropositive patients following single-dose administration of THALOMID™ (thalidomide) capsules.¹

Patients With Hansen's Disease

Analysis of data from a small study in patients with Hansen's disease suggests that these patients, relative to healthy subjects, may have an increased bioavailability of thalidomide.¹ The increase is reflected both in an increased AUC and in increased peak plasma levels.¹ The significance of this apparent increase is unknown.

Impaired Renal or Hepatic Function

The pharmacokinetics of thalidomide in patients with renal dysfunction or hepatic impairment have not been determined.¹

Age Effects

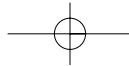
Analysis of the data from pharmacokinetic studies in healthy volunteers and patients with Hansen's disease ranging in age from 20 to 69 years does not reveal any age-related changes.¹ No pharmacokinetic data are available in children younger than 18 years of age.¹

Gender Effects

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.¹

Race Effects

Pharmacokinetic differences due to race have not been evaluated.¹



THERAPEUTIC USE IN ERYTHEMA NODOSUM LEPROSUM

THALOMID™ (thalidomide): Indications

THALOMID™ (thalidomide) is indicated for the acute treatment of the cutaneous manifestations of moderate to severe ENL.¹ THALOMID™ (thalidomide) is not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis.¹ THALOMID™ (thalidomide) also is indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence.¹

Erythema Nodosum Leprosum

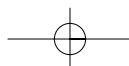
Epidemiology

Leprosy (Hansen's disease) is a chronic infectious disease caused by *Mycobacterium leprae*, an extremely slow-growing bacillus.^{1,25,26} An estimated 6 million people worldwide have leprosy, of whom 3 million remain untreated.^{1,25,26} Leprosy is endemic in Asia, Africa, Latin America, and the Pacific.^{1,26} In the United States, there are an estimated 7,000 patients with the disease.^{1,26} About 200 newly diagnosed cases are reported in the United States each year.^{1,25,26} Leprosy is associated with poverty, rural residence, and at times in North America, armadillo contact.^{1,26} Cases from Hawaii, Louisiana, California, and Texas continue to be reported of individuals without a history of previous travel to areas where leprosy is endemic.^{1,27}

Pathophysiology

ENL is a systemic disorder that commonly results from antileprosy treatment and is associated with fever, neuritis, malaise, anorexia, leukocytosis, weight loss, and anemia.^{1,13} It may be acute or chronic. Histologically, ENL is an acute vasculitis or panniculitis that most likely results from immune complex deposition following death of *M leprae* bacteria and is associated with increased numbers of helper T cells, IL-2, and IFN- γ and loss of suppressor T-cell activity.^{1,10,26,28-30} ENL can be quite debilitating and in extreme cases may cause severe morbidity.¹ The most common clinical manifestation is crops of painful erythematous nodules of the skin and subcutaneous tissues.^{1,11,13,26,29} If severe, pustules develop, which can ulcerate, causing suppurative wounds and subsequent scarring.^{1,28}

Fever, weight loss, and overall debility may result from macrophage production of cytokines, especially TNF- α , suggesting that TNF- α production may mediate the immunopathologic manifestations of ENL.^{1,17} ENL is associated with elevated levels of TNF- α .^{1,11,17,18}



Physical Sequelae

ENL causes progressive synovitis, nephritis, iritis, lymphadenitis, and epididymo-orchitis.¹ Much of the morbidity and deformity of leprosy is a consequence of ENL neuritis.¹ Progressive nerve damage may culminate in muscle weakness and insensitivity and, in later stages, clawed hands and plantar ulcers that often necessitate amputations of distal extremities.¹ Skin lesions can lead to obvious scarring with either hypopigmentation or hyperpigmentation and may result in significant marking of the patient.¹

Efficacy of THALOMID™ (thalidomide) in 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 US Public Health Service.¹ The published literature describes the treatment of 6,272 patients over a 30-year period, and the United States IND 11,359 database describes clinical experience in the therapy of 1,368 patients from 1978 to 1994 and represents 4,799 patient-years of data.¹ The published literature on the efficacy of thalidomide for the treatment of ENL includes six controlled clinical trials, 26 open-label clinical trials, and 15 case reports, involving a total of 1,848 patients.¹

Treatment of Cutaneous Manifestations

Two double-blind, randomized, controlled clinical trials reported the dermatologic response to a 7-day course of thalidomide 100 mg (four times daily) or control.^{31,32} Dosage was lower for patients under 50 kg. The results of these trials demonstrated that thalidomide was more effective than aspirin or placebo in treating the cutaneous manifestations of the disease (Table 2).^{1,31,32}

Table 2. Double-blind, randomized, controlled clinical trials of thalidomide in patients with ENL: Cutaneous response^{1,31,32}

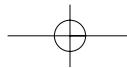
Investigator	No. of Patients	No. Treatment Courses*	Percent Responding [†]	
			Thalidomide	Comparative Agent
<i>Iyer et al</i> ³¹	92	204	75%	25% ^{††}
<i>Sheskin and Convit</i> ³²	52	173	66%	10% [‡]

* In patients with cutaneous lesions.

[†] Iyer et al: Complete response or lesions absent. Sheskin and Convit: Complete improvement + "striking" improvement (ie, >50% improvement).

^{††} Comparative agent = aspirin.

[‡] Comparative agent = placebo.



Waters reported the results of two double-blind, randomized, placebo-controlled, crossover trials in a total of 10 hospitalized steroid-dependent patients with chronic ENL treated with thalidomide 100 mg or placebo three times daily for 4- and 6-week periods.³³ All patients also received dapsone. The primary endpoint was reduction in weekly steroid dosage. After 4 and 6 weeks of treatment, 4/5 and 8/8 of patients receiving thalidomide had a reduction in steroid dosage, compared with 0/4 and 1/8 of those receiving placebo, respectively (Table 3).^{1,33}

Table 3. Double-blind, randomized, placebo-controlled crossover trial of thalidomide in patients with ENL: Reduction in steroid dosage^{1,33}

Investigator	Treatment Duration	No. of Patients	No. Responding	
			Thalidomide	Placebo
<i>Waters</i> ³³	4 weeks	9	4/5	0/4
	6 weeks (crossover)	8	8/8	1/8

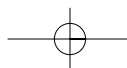
These data demonstrate that thalidomide is effective for the treatment of cutaneous manifestations of moderate to severe ENL.¹ Where the condition is complicated with neuritis, concomitant use of steroids is indicated until the neuritis has resolved. In most patients, response to thalidomide was observed within days and complete resolution of signs and symptoms to the reactional state was observed within 1 to 2 weeks of treatment initiation.¹ Skin lesions and fever responded most rapidly.¹ In early clinical experience with thalidomide, including all six controlled clinical trials, the drug was administered at a dose of 300 to 400 mg/d.¹ More recent experience has demonstrated the effectiveness of thalidomide 100 to 200 mg/d for the initial control of ENL.¹ In the first year of therapy for patients treated under IND 11,359, thalidomide 100 and 200 mg/d were the mean daily effective doses for 66% and 28% of patients, respectively.¹

Prevention of Relapse

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 US Public Health Service.¹ A subset of patients with ENL controlled on thalidomide demonstrated repeated relapse upon drug withdrawal and remission with reinstatement of therapy.¹ Following acute treatment, maintenance dosing with thalidomide 25 to 200 mg/d has proven effective in preventing recurrent reactions.¹

Summary of Investigational Use Experience: US Public Health Service IND 11,359

The investigational use of thalidomide for the treatment of ENL in the United States is conducted under the US Public Health Service IND 11,359.¹ This mechanism of use was initiated in 1975.¹



Annually, physicians treating patients with thalidomide provide demographic and dosing information and rate the patient's response to treatment during the previous year.¹ The response categories include "good" (complete ENL control), "fair" (partial ENL control), "poor" (no response), "unknown," and "lost to follow-up."¹ Complete ENL control indicates that ENL is either totally controlled or patients experience only an occasional ENL skin lesion without fever or other systemic manifestations of reaction.¹

Clinical Results

Initial Response to Thalidomide The demographic characteristics of the patient population reflected in the compassionate use experience are shown in Table 4. Of the 1,368 patients, 34 had either an "unknown" response or were "lost to follow-up."¹ Therefore, 1,334 patients with a response determination during the initial year of treatment are included in the response analysis.¹ Complete control of ENL was reported in 1,067 (80%) patients (Table 5).¹ Only 2% had no response to thalidomide treatment during the initial year.¹

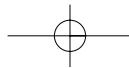
Continued Response to Thalidomide Complete control was maintained with continued treatment.¹ Of patients with complete ENL control during the initial year, 93% maintained complete control at year 3 (mean duration of the initial treatment course).¹ Though the number of patients diminished, complete control was maintained in more than 83% of patients during the entire 14-year period included in the database.¹ Of the patients whose initial response was partial ENL control during the initial year, complete control was achieved at years 2 and 3 in 59% and 67% of patients, respectively.¹ After reporting year 5, complete control was achieved and maintained in approximately 80% of patients.¹

Dose Response Of the 900 patients who received thalidomide \leq 100 mg/d during the initial year of reporting, 747 (83%) had a complete response (Table 6).¹ Partial control was achieved in 12.6% of patients.¹ Of the 377 patients who received thalidomide 101 to 200 mg/d, a complete response was achieved in 258 (68.4%).¹ Similarly, of the 59 patients

Table 4. Investigational use experience in ENL 1978-1994 (US Public Health Service IND 11,359): Patient characteristics¹

	N (%)
Age (y)	
< 18	20 (1.5)
18-64	1,212 (88.6)
\geq 65	136 (9.9)
Gender	
Male	1,067 (78.0)
Female	301 (22.0)
Race	
Hispanic	632 (46.2)
Asian	502 (36.7)
Caucasian	162 (11.8)
Black	52 (3.8)
Other	20 (1.5)
Disease classification	
LL	1,156 (84.5)
BL	212 (15.5)
Mean duration of Hansen's disease prior to study entry (y)	
All patients (n=1,337)	5.8
Patients with prior ENL episodes (n=485)	5.3
Patients without prior ENL episodes (n=822)	6.1

LL = lepromatous leprosy; BL = borderline lepromatous leprosy; ENL = erythema nodosum leprosum.



who received thalidomide 201 to 300 mg/d, 40 (67.8%) achieved complete control of their ENL reactions.¹

These data indicate that a higher complete control rate was achieved in patients receiving thalidomide doses \leq 100 mg/d compared with those receiving higher doses.¹ However, this may reflect the fact that patients receiving higher thalidomide doses generally had more severe ENL reactions.¹

Table 5. Investigational use experience in ENL 1978-1994 (US Public Health Service IND 11,359): Response to thalidomide during the initial year¹

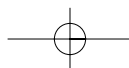
	N (%)
Total No. patients	1,334 (100.0)
Complete control	1,067 (80.0)
Partial control	239 (17.9)
No response	28 (2.1)

Clinical Trials Summary

The diverse sources of information on the use of thalidomide to control ENL demonstrate its efficacy in this disease.¹ The substantial clinical experience with thalidomide provides the basis for the global clinical use of thalidomide as the agent of choice for control of chronic, recurrent ENL in men and in women of non-childbearing potential.¹ Clinical evidence demonstrates the effectiveness of thalidomide in rapidly ameliorating the signs and symptoms of ENL in a high percentage of treated patients when used in doses of 300 to 400 mg/d.¹ In some patients, thalidomide doses of 100 to 200 mg/d also are effective.¹ Thalidomide maintenance doses of 50 to 200 mg/d are effective in preventing the recurrence of signs and symptoms of ENL.¹ Maintenance doses as low as 2.5 mg/d have apparently been effective in some patients.¹

Summary of Key Efficacy Results

- Thalidomide is effective for the control of the cutaneous manifestations of moderate to severe ENL in most patients. High response rates to thalidomide have been reported in patients receiving antileprosy therapy, those who are seriously ill with fevers, and those who were previously corticosteroid-dependent.
- In most patients, response to thalidomide is observed within days, with complete resolution of signs and symptoms within 1 to 2 weeks of treatment initiation.
- Thalidomide also is effective in the prevention of ENL relapse.
- Concomitant use of steroids is indicated in the presence of neuritis.



SAFETY CONSIDERATIONS AND ADVERSE EFFECTS

Overview

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 CAN CAUSE SEVERE BIRTH DEFECTS.

Thalidomide has been studied in controlled clinical trials in patients with ENL and in those who are HIV-seropositive.¹ In addition, thalidomide has been administered investigationally for more than 20 years in numerous indications.¹ The most serious toxicity associated with thalidomide is its documented teratogenicity. The risk of severe birth defects, primarily phocomelia or death to the fetus, is extremely high during the critical period of pregnancy (35 to 50 days after the last menstrual period). Peripheral neuropathy is a common, potentially severe side effect that may be irreversible.¹ Caution should be exercised in patients with preexisting neuropathy and treatment should be discontinued if peripheral neuropathy develops or worsens. Hypersensitivity 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. Laboratory abnormalities also have been associated with the use of thalidomide. Neutropenia ($ANC < 750/mm^3$) has been observed, especially in HIV-seropositive patients. Increases in viral load (median change = 0.42 \log_{10} copies HIV RNA/mL, $P=0.04$ compared to placebo) have been observed in HIV-seropositive patients.^{1,12} Somnolence, dizziness, and rash are the most commonly observed adverse events associated with thalidomide use.¹ Patients receiving THALOMID™ (thalidomide) should be advised to take the drug only as prescribed and not to share the medication with anyone else.¹

Adverse Experiences

Incidence in Controlled Clinical Trials

Treatment-emergent signs and symptoms that occurred in patients with ENL who received thalidomide in controlled clinical trials are shown in Table 7.¹ Doses ranged from 50 to 300 mg/d.¹ All adverse events were mild to moderate in severity, and none resulted in treatment discontinuation.¹

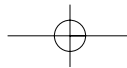


Table 6. Investigational use experience in ENL 1978-1994 (US Public Health Service IND 11,359):
Thalidomide dose response during the initial year of study enrollment¹

Thalidomide Dose* (mg/d)	Complete Control n (%)	Partial Control n (%)	No Response n (%)	Lost to Follow-Up n (%)	Unknown n (%)
1-100 (n=900)	747 (83.0)	113 (12.6)	16 (1.8)	11 (1.2)	13 (1.4)
101-200 (n=377)	258 (68.4)	103 (27.3)	8 (2.1)	3 (0.8)	5 (1.3)
201-300 (n=59)	40 (67.8)	17 (28.8)	1 (1.7)	0	1 (1.7)
301-400 (n=12)	6 (50.0)	6 (50.0)	0	0	0

*Multiple drug sources.

Other Adverse Events Observed in ENL Patients

Thalidomide, in doses up to 400 mg/d, has been administered investigational in the United States over a 19-year period in 1,465 patients with ENL; the published literature describes the treatment of an additional 1,678 patients.¹ To provide a meaningful estimate of the proportion of individuals experiencing adverse events, similar types of events were grouped using modified COSTART terminology.¹ All reported events are included except those listed in Table 7, those too general to be informative, and those not reasonably associated with thalidomide administration.¹ Due to the fact that these data were collected from uncontrolled studies, the incidence rates cannot be determined.¹ No causal relationship between thalidomide and these events can be conclusively determined at this time.

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

Cardiovascular System: bradycardia, hypertension, hypotension, peripheral vascular disorder, tachycardia.

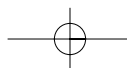
Digestive System: anorexia, appetite increase/weight gain, dry mouth, dyspepsia, enlarged liver, eructation, flatulence, increased liver function tests, intestinal obstruction, vomiting.

Hemic/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.¹

Musculoskeletal: 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.

Adverse Events in HIV-Seropositive Patients

Treatment-emergent adverse events that occurred in at least three of the thalidomide-treated HIV-seropositive patients with wasting who participated in an 8-week, placebo-controlled clinical trial are shown in Table 7.¹ Events that were more frequent in the placebo-treated group are not included.¹

Other Adverse Events Observed in HIV-Seropositive Patients

In addition to controlled clinical trials, thalidomide has been used in uncontrolled studies in 145 HIV-seropositive patients.¹ Less frequent adverse events that have been reported in these HIV-seropositive patients treated with thalidomide were grouped into a smaller number of standardized categories using modified COSTART dictionary/terminology.¹ Adverse events listed in Table 7 also are included in the following list; all other reported adverse events also are included, except those too general to be informative and those not reasonably associated with thalidomide administration.¹

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.

Table 7. Summary of adverse events reported in Celgene-sponsored controlled clinical trials¹

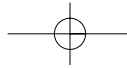
Body System/Adverse Event	In All ENL Patients	In ≥ 3 HIV-Seropositive Patients*		
	Thalidomide 50-300 mg/d (n=24) (%)	Thalidomide 100 mg/d (n=36) (%)	Thalidomide 200 mg/d (n=32) (%)	Placebo (n=35) (%)
<i>Body as a whole</i>	16 (66.7)	18 (50.0)	19 (59.4)	13 (37.1)
Abdominal pain	1 (4.2)	1 (2.8)	1 (3.1)	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)
<i>Digestive system</i>	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)
Abnormal LFTs	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
<i>Hemic and lymphatic system</i>	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)
<i>Metabolic and endocrine disorders</i>	1 (4.2)	8 (22.2)	12 (37.5)	8 (22.9)
Peripheral edema	1 (4.2)	3 (8.3)	1 (3.1)	0
Hyperlipidemia	0	2 (5.6)	3 (9.4)	1 (2.9)
Increased SGOT	0	1 (2.8)	4 (12.5)	2 (5.7)

Table 7. (continued).

Body System/Adverse Event	In All ENL Patients	In ≥ 3 HIV-Seropositive Patients*		
	Thalidomide 50-300 mg/d (n=24) (%)	Thalidomide 100 mg/d (n=36) (%)	Thalidomide 200 mg/d (n=32) (%)	Placebo (n=35) (%)
<i>Nervous system</i>	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
<i>Respiratory system</i>	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)
<i>Skin and appendages</i>	10 (41.7)	17 (47.2)	18 (56.3)	19 (54.3)
Acne	0	4 (11.1)	1 (3.1)	0
Fungal dermatitis	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)
Maculopapular rash	1 (4.2)	6 (16.7)	6 (18.7)	2 (5.7)
Sweating	0	0	4 (12.5)	4 (11.4)
<i>Urogenital system</i>	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

LFTs=liver function tests; SGOT = serum glutamic-oxaloacetic transaminase.

* Adverse events reported in at least 3 patients enrolled in the HIV-wasting study.



Digestive System: cholangitis, colestatic 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 System: aplastic anemia, macrocytic anemia, megaloblastic anemia, microcytic anemia.

Metabolic and Endocrine System: avitaminosis, bilirubinemia, dehydration, hypercholesterolemia, 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.

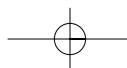
Respiratory System: apnea, bronchitis, lung disorder, lung edema, pneumonia (including *Pneumocystis carinii* pneumonia), rhinitis.

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.

Other Adverse Events in the Published Literature or Reported From Other Sources

Additional adverse events identified either in the published literature or from spontaneous reports from other sources include acute renal failure, amenorrhea, aphthous stomatitis, bile duct obstruction, carpal tunnel syndrome, 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.¹



Teratogenicity

The most serious toxicity associated with thalidomide is its documented teratogenicity.^{1,2} If thalidomide is taken during pregnancy, it can cause severe birth defects or death to the unborn baby.¹ Thalidomide should never be used by women who are pregnant or who could become pregnant while taking the drug.¹ Even a single dose (one capsule [50 mg]) taken by a pregnant woman can cause severe birth defects.¹

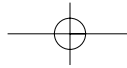
The risk of severe birth defects, primarily phocomelia, or death to the fetus is extremely high during the critical period of pregnancy.^{1,2,23} The critical period is estimated, depending on the source, to range from 35 to 50 days after the last menstrual period.^{1,2,34} The risk of other potentially severe birth defects outside this critical period is unknown, but may be significant.^{1,2} THALOMID™ (thalidomide) must not be used at any point during pregnancy.¹

Major human fetal abnormalities related to thalidomide administration have been documented and include amelia (absence of limbs), phocomelia (defective shortened limbs, “flippers”), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia [absence of ears], microtia [small ears], micropinna [small or absent external auditory canals]), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects.^{1,2,34-37} Alimentary tract, urinary tract, and genital malformations also have been documented.^{1,2,35,36} Mortality at or shortly after birth is approximately 40%.¹

The exact mechanism of teratogenicity has not been conclusively determined, although a number of biochemical, cellular, and tissue- or organ-level mechanisms have been proposed for thalidomide, as well as for some of its metabolites.^{1,2,35,38} Thalidomide has been shown to cause subtle tissue changes in the limb bud mesenchyme shortly after administration of teratogenic doses to New Zealand white rabbits.³⁵ An analysis of a series of Australian thalidomide children suggested that the underlying organization of thalidomide anomalies was segmental, possibly due to an action on the segmental sensory neurons of the embryo.^{1,35} This is supported by studies in rabbits in which thalidomide interfered with the normal process of neuronal maturation in the dorsal root ganglia of the embryo.^{1,35} This observation suggests that the underlying pathology of the limb deformities due to thalidomide is the result of embryonic neuropathy.^{1,35}

Peripheral Neuropathy

Peripheral neuropathy is a common, potentially severe side effect of treatment with THALOMID™ (thalidomide) that may be irreversible.¹ Peripheral neuropathy generally occurs following chronic use over a period of months; however, reports following relatively short-term use also exist.¹ The correlation with cumulative dose is unclear.¹ Symptoms may occur some time after thalidomide treatment has been stopped and may resolve slowly, or not at all.¹ Few reports of neuropathy have arisen in the treatment of ENL, despite long-term thalidomide treatment.¹

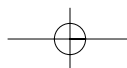


However, the inability clinically to differentiate thalidomide neuropathy from the neuropathy often seen in Hansen's disease makes it difficult to determine accurately the incidence of thalidomide-related neuropathy in ENL patients treated with thalidomide. Thalidomide-associated peripheral neuropathy is characterized as a distal axonopathy with the long and large diameter motor and sensory axons of the feet and hands being affected.^{1,3,34,39} Degeneration gradually moves proximally (dying back) towards the nerve cell body.^{34,39,40} The initial complaint is typically a numbness of the toes and feet, sometimes described as an unpleasant and distressing feeling of "tightness around the feet."^{1,3,39} There is a superficial sensory loss (sensitivity to light touch and pinprick) in the feet and hands.^{1,40} Muscle cramps may occur, although actual muscle weakness is infrequent and mild when present.³⁹ Patients may experience a variety of clinical symptoms, including symmetric sensorimotor neuropathy, painful paresthesias in the hands and feet, distal hypoesthesia, proximal weakness in the lower limbs, slight postural tremor, leg cramps, absent ankle jerks, brittle nails, and redness of the palms.^{3,39,41,42} If therapy continues, paresthesias of the feet will gradually become permanent and progress up the legs.^{1,34} The same symptoms will occur in the hands and progress proximally.

Thalidomide peripheral neuropathy is characterized by axonal degeneration without demyelination, affecting mainly sensory fibers in the lower limbs.³⁴ In a study evaluating the electrophysiologic effects associated with thalidomide peripheral neuropathy in 13 patients with discoid lupus erythematosus, the most prominent electrophysiologic alteration was a decreased sensory nerve action potential (SNAP) amplitude in the sural nerve.^{34,42} Improvement of clinical symptoms was not associated with resolution of electrophysiologic abnormalities.⁴² For two patients, abnormalities were evident more than 1 year after terminating thalidomide treatment, despite the disappearance of clinical symptoms.⁴²

Although many investigators have concluded that there is no clear correlation between the onset of neuropathy with the disease state, metabolic rate, total thalidomide dose, or duration of treatment,^{34,39} others have suggested that symptoms, signs, and electrophysiologic data can be correlated with total cumulative thalidomide dose.⁴¹ Wulff et al indicated that peripheral neuropathy is more likely when total doses exceed 40 to 50 g.⁴³ Fullerton and O'Sullivan suggested that total dose was better correlated with peripheral neuropathy than total treatment duration, and symptoms were more severe with higher total doses.³⁹ Older patients (≥ 60 years) may be more susceptible to thalidomide-associated neuropathy than younger patients.^{1,39} Patients younger than 60 years of age tend to recover more quickly and completely than those older than 60.³⁹

In a 5.5-year prospective study, 50 patients receiving thalidomide for various dermatologic disorders underwent clinical evaluations monthly for 6 months and then every 3 months for the remainder of the study.⁴⁴ Electromyographic studies were performed initially and then every 6 months. Results showed that 89% of patients who developed neuropathy were older than 36 years of age and received more than 14 g of thalidomide.⁴⁴



Patients younger than 56 years of age who received less than 14 g were not likely to develop neuropathy. Based on these findings, cumulative dose and age both appear to be important in the occurrence of thalidomide-associated neuropathy.⁴⁴

It also has been suggested that patients who exhibit a slow acetylation phenotype may be more susceptible to thalidomide-induced neuropathy, although this correlation has not been fully investigated.⁴⁵

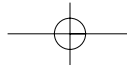
THALOMID™ (thalidomide) should be used with caution in patients with preexisting neuropathy.¹ Patients should be examined at monthly intervals for the first 3 months of thalidomide therapy to enable the clinician to detect early signs or symptoms of peripheral neuropathy, which include numbness, tingling, or pain in the feet or hands.¹ Patients should be regularly counseled, questioned, and evaluated for signs and symptoms of peripheral neuropathy. Patients should be evaluated periodically thereafter during treatment.¹ Consideration should be given to electrophysiologic testing, consisting of measurement of SNAP amplitudes at baseline and every 6 months thereafter in an effort to detect asymptomatic neuropathy.¹ If symptoms develop, THALOMID™ (thalidomide) should be stopped immediately to limit further damage.¹ Usually, treatment should only be reinitiated if the neuropathy returns to baseline status.¹ Medications known to be associated with neuropathy should be used with caution in patients receiving THALOMID™ (thalidomide).¹

Sedation

Thalidomide frequently causes drowsiness and somnolence.^{1,46} Somnolence and dizziness appear more frequently at doses of 200 to 400 mg than at lower doses.^{1,46} An analysis of thalidomide compassionate use experience in ENL patients showed that 11% of patients complained of somnolence.¹ In patients infected with HIV, drowsiness, dizziness, and mood changes occurred in 33% to 100% of patients.³⁴

Administering thalidomide in the evening can minimize drowsiness.¹ For patients who require higher doses, the dose can be increased by 100 to 200 mg/d every 4 to 7 days.¹ Tolerance to the sedative effects usually occurs over time.¹

Patients should be instructed to avoid situations in which drowsiness may be a problem and not to take other medications that may cause drowsiness without adequate medical advice.¹ 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.¹ Patients also should be advised that THALOMID™ (thalidomide) may cause dizziness or orthostatic hypotension; therefore, they should sit upright for a few minutes prior to standing from a recumbent position.¹



Other Adverse Events

Laboratory Abnormalities

Neutropenia

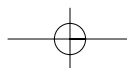
Decreased white blood cell (WBC) counts, including neutropenia, have been reported in association with the clinical use of thalidomide.^{1,46} Thalidomide treatment should not be initiated in patients who have an absolute neutrophil count (ANC) of $< 750/\text{mm}^3$.¹ WBC count and differential should be monitored on an ongoing basis, especially in patients who may be more prone to neutropenia, such as HIV-seropositive patients.¹ If the ANC falls to $< 750/\text{mm}^3$ while the patient is receiving thalidomide, the patient's medication regimen should be evaluated, and if the neutropenia persists, consideration should be given to withholding thalidomide if clinically appropriate.¹

HIV-Viral Load

Increases in viral load of 0.3 to 0.4 \log_{10} copies HIV RNA/mL have been observed in HIV-seropositive patients.¹² 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; $P = 0.04$ versus placebo).^{1,12} A similar trend was observed in a second, unpublished study conducted in patients who were HIV-seropositive.¹ The clinical significance of this increase is unknown. Both studies were conducted prior to availability of highly active anti-retroviral therapy.¹ In HIV-seropositive patients, viral load should be measured after the first and third months of treatment and every 3 months thereafter.¹

Rash

Hypersensitivity to THALOMID™ (thalidomide) has been reported.^{1,46,47} The incidence of rash appears to vary depending on the treatment population. In ENL, rash was reported infrequently ($< 1\%$) in the two largest patient series (more than 2,500 patients).¹ Rash has been reported in patients with chronic graft-versus-host disease (GVHD; 20%, 16/80); cancers; prurigo nodularis; and HIV aphthous ulcers (24%, 7/29) treated with thalidomide.^{1,34,46,48} In one study, patients with GVHD who developed skin rashes with the start of thalidomide treatment had a higher incidence of two poor risk factors, prior thrombocytopenia and progressive presentation of chronic GVHD.⁴⁶ HIV patients appear to experience rash more frequently,²⁰ and in general seem to have a greater hypersensitivity to drugs.³⁴ Some investigators have reported that patients who developed rash had lower CD4 T-cell



counts (17 cells/mm³) than those who did not develop rash (CD4 count, 216 cells/mm³; $P < 0.005$).²⁰ Eosinophilia (5,104 to 5,579 eosinophils/mm³) in association with rash also has been reported.⁴⁸

Signs and symptoms have included erythematous macular rash possibly associated with fever, tachycardia, and hypotension.^{1,47} The rash is described as a pruritic erythematous macular rash over the trunk and back, but not in the axillae and groin.^{1,20,48} It most frequently occurs 2 to 10 days after treatment initiation.¹ If severe, hypersensitivity may necessitate interruption of therapy.¹ Discontinuing therapy as soon as the rash is recognized may bring prompt relief^{20,48}; the rash is usually easily managed with antihistamines, if needed.¹ Continuation of therapy may result in a more severe reaction.^{20,48} If the reaction recurs when dosing is resumed, THALOMID™ (thalidomide) should be discontinued.¹

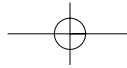
Gastrointestinal

Constipation is one of the more frequently encountered adverse effects of thalidomide, with a reported frequency ranging from 3% to 30%.^{1,34} Management consists of mild laxatives (eg, milk of magnesia, lactulose, psyllium) and, if necessary, dose reduction.¹

Contraindications

Due to its known human teratogenicity, even following a single dose, THALOMID™ (thalidomide) is contraindicated in pregnant women and women capable of becoming pregnant.¹ When there is no alternative treatment, women of childbearing potential may be treated with THALOMID™ (thalidomide) provided adequate precautions are taken to avoid pregnancy.¹ Women must commit to either continuously abstain from heterosexual sexual intercourse or to use two methods of birth control, which includes at least one highly effective method (eg, intrauterine device [IUD], hormonal contraception, tubal ligation, partner's vasectomy) and one additional effective method (eg, latex condom, diaphragm, cervical cap), beginning at least 4 weeks prior to initiating treatment with THALOMID™ (thalidomide), during therapy, and continuing for 4 weeks following treatment discontinuation, even where there has been a history of infertility. The only exceptions are in women who have had a hysterectomy or had no menses or have been postmenopausal for at least 24 months.¹ If hormonal or IUD contraception is medically contraindicated, two other effective or highly effective methods may be used.¹

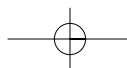
Women of childbearing potential being treated with THALOMID™ (thalidomide) should undergo pregnancy testing (sensitivity ≥ 50 mIU/mL) even if continuous abstinence is the chosen method of birth control.¹ The test should be performed within the 24 hours before beginning therapy and then weekly during the first month of use, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular 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 does occur during treatment, the drug 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.¹ 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.¹ Animal studies to characterize the effects of thalidomide on late-stage pregnancy have not been conducted.¹

THALOMID™ (thalidomide) is contraindicated in WOMEN of childbearing potential and sexually mature males unless the PATIENT MEETS ALL OF THE FOLLOWING CONDITIONS¹:

- Men and women must understand and reliably carry out instructions.
- Men and women must be capable of complying with the mandatory contraceptive measures, pregnancy testing (women only), patient registration, and patient survey as described in the System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.™*) program.
- Men and women must have received both oral and written warnings of the hazards of taking THALOMID™ (thalidomide) and exposing a fetus to the drug.
- A woman must have received both oral and written warnings of the risk of possible contraception failure and the need to use two reliable forms of contraception simultaneously unless continuous abstinence 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 (ie, who have had menses at sometime in the preceding 24 consecutive months) are considered to be women of childbearing potential. She must acknowledge in writing her understanding of these warnings and of the need for using two reliable contraceptive methods for 4 weeks prior to starting thalidomide therapy, during therapy, and for 4 weeks after stopping therapy.
- A man must have 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 a successful vasectomy. He must acknowledge in writing his understanding of these warnings and of the need for using barrier contraception (latex condoms), even if he has undergone a successful vasectomy, when having sexual intercourse with women of childbearing potential.
- A woman must have a negative pregnancy test with a sensitivity of ≥ 50 mIU/mL within the 24 hours before beginning therapy.
- If the patient is between 12 and 18 years of age, the parent or legal guardian must have read this material and agreed to ensure compliance with the above.



THALOMID™ (thalidomide) is contraindicated in patients who have demonstrated hypersensitivity to the drug or its components.¹

Pediatric Precautions

Safety and effectiveness of THALOMID™ (thalidomide) in children younger than 12 years have not been established.¹

Geriatric Precautions

Systematic studies evaluating the use of THALOMID™ (thalidomide) in geriatric patients have not been conducted.¹ Thalidomide has been used in clinical trials in patients up to 90 years of age.¹ Adverse events in patients older than 65 years of age did not differ from those reported for younger individuals.¹

Carcinogenicity, Mutagenicity, and Impairment Effects on Fertility

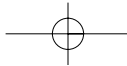
Long-term carcinogenicity tests with thalidomide have not been conducted.¹ Thalidomide gave no evidence of mutagenic effects when assayed in in vitro bacterial (*Salmonella typhimurium* and *Escherichia coli*, Ames mutagenicity test), in vitro mammalian (AS52 Chinese hamster ovary cells, AS52/XPRT mammalian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

Use in Nursing Mothers

It is not known whether THALOMID™ (thalidomide) is excreted in human milk.¹ Because many drugs are excreted in human milk and because of the potential for serious adverse reactions to THALOMID™ (thalidomide) in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman.

Drug Interactions

Drug-drug interactions with THALOMID™ (thalidomide) have not been systematically studied, except for hormonal contraceptives as described below.^{1,34} At physiologic pH, thalidomide spontaneously hydrolyzes nonenzymatically.¹ In a study of the metabolism of thalidomide in patients with Hansen's disease, no metabolites were found in plasma and less than 0.01% of the dose was excreted in the urine as 4-OH-thalidomide.¹ In vitro studies using a large range of human cloned cytochrome-P450 enzymes, rat liver homogenates, and human liver homogenates also failed to reveal any appreciable evidence of metabolism.¹



Oral Contraceptives

In 10 healthy women, the pharmacokinetic profiles of norethindrone and ethinyl estradiol following a single dose containing norethindrone acetate 1 mg and ethinyl estradiol 75 µg were studied. The results were similar with and without coadministration of THALOMID™ (thalidomide) 200 mg/d to steady-state levels.¹

Drugs Associated With Peripheral Neuropathy

Medications known to be associated with peripheral neuropathy should be used with caution in patients receiving THALOMID™ (thalidomide).¹

CNS Depressants

THALOMID™ (thalidomide) has been reported to enhance the sedative activity of barbiturates, alcohol, chlorpromazine, and reserpine.^{1,34}

Important Non-THALOMID™ (thalidomide) Interactions

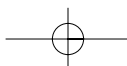
Concomitant use of HIV-protease inhibitors, griseofulvin, rifampin, rifabutin, phenytoin, or carbamazepine with hormonal contraceptive agents may reduce the effectiveness of the contraception.¹ Therefore, women requiring treatment with one or more of these drugs should use two OTHER effective or highly effective methods of contraception or abstain from reproductive heterosexual sexual intercourse.¹

Overdosage

There have been three cases of thalidomide overdose reported, all of which were attempted suicides.¹ There have been no reported fatalities following thalidomide doses of up to 14.4 g, and all patients recovered without reported sequelae.¹

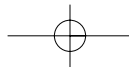
Drug Abuse and Dependence

Physical and psychological dependence have not been reported in patients taking THALOMID™ (thalidomide).¹ However, as with other tranquilizers/hypnotics, thalidomide too has been reported to create in patients habituation to its soporific effects.



Safety Considerations and Adverse Effects Summary

- A single dose of THALOMID™ (thalidomide) can result in severe birth defects or death to the fetus. The use of effective contraception is essential for men as well as women because thalidomide may be present in semen or sperm. Routine pregnancy testing is required as well as participation in the System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.™*) program by all prescribers, pharmacists, and patients.
- Peripheral neuropathy is a common, potentially severe side effect of treatment with THALOMID™ (thalidomide) that may be irreversible. Symptoms may occur some time after treatment has been discontinued and may resolve slowly or not at all. Few reports have arisen in the treatment of ENL, despite long-term thalidomide treatment.
- Decreased WBC counts, including neutropenia, have been reported in association with clinical use of THALOMID™ (thalidomide).
- Drowsiness is the most frequent adverse effect associated with THALOMID™ (thalidomide) use. This effect can be minimized by administration at bedtime. Daytime drowsiness, if present, usually diminishes after several weeks.
- The most common adverse events in patients with ENL who received thalidomide in controlled clinical trials were somnolence, rash, and pain. All adverse events were mild to moderate in severity, and none resulted in treatment discontinuation.
- Constipation is a mild and infrequent side effect that can generally be controlled with stool softeners and/or a mild laxative.
- An erythematous macular rash can occur after 2 to 10 days of therapy. It can be managed by dose reduction and, if necessary, administering antihistamines. If it does not resolve, therapy should be discontinued.



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.

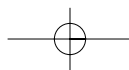
Acute ENL Reaction

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

Severe ENL Reaction

In patients with a severe cutaneous ENL reaction or in those who have previously required higher doses to control the reaction, THALOMID™ (thalidomide) may be initiated at higher doses, up to 400 mg/d.¹ THALOMID™ (thalidomide) should be administered once daily at bedtime or in divided doses with water, and should be taken at least 1 hour after meals.¹ In patients with moderate to severe neuritis associated with a severe ENL reaction, corticosteroids may be initiated concomitantly with THALOMID™ (thalidomide).¹ Corticosteroid usage can be tapered and discontinued when the neuritis has ameliorated.¹

THALOMID™ (thalidomide) should be usually continued until signs and symptoms of active reaction have subsided, usually at least 2 weeks.¹ The daily THALOMID™ (thalidomide) dose can then be tapered in 50-mg decrements every 2 to 4 weeks.¹ Patients who have a documented history of requiring prolonged maintenance treatment to prevent the recurrence of cutaneous ENL or who experience a flare during tapering should be maintained on the minimum dose necessary to control the reaction.¹ Tapering of THALOMID™ (thalidomide) and discontinuation of the drug should be attempted every 3 to 6 months in 50-mg decrements every 2 to 4 weeks.¹



Summary of Dosage and Administration for Cutaneous ENL

- For an episode of cutaneous ENL, THALOMID™ (thalidomide) 100 to 300 mg/d should be administered once daily and continued until signs and symptoms have subsided, usually at least 2 weeks.
- For severe reactions, THALOMID™ (thalidomide) doses as high as 400 mg/d may be needed.
- After signs and symptoms have subsided, the daily THALOMID™ (thalidomide) dose should be tapered in 50-mg decrements every 2 to 4 weeks. Patients with a documented history of requiring prolonged maintenance treatment to prevent ENL recurrence or who experience a flare during tapering should be maintained on the minimum dose necessary to control the reaction. In these patients, a THALOMID™ (thalidomide) tapered withdrawal should be attempted every 3 to 6 months.
- In patients with moderate to severe neuritis associated with a severe ENL reaction, corticosteroids should be started concomitantly with THALOMID™ (thalidomide). Steroid usage can be tapered and discontinued when the neuritis has ameliorated.

SYSTEM FOR THALIDOMIDE EDUCATION AND PRESCRIBING SAFETY (*S.T.E.P.S.*TM)

Description

The System for Thalidomide Education and Prescribing Safety, *S.T.E.P.S.*TM, is a multicomponent system designed to help ensure that fetal exposure to THALOMIDTM (thalidomide) does not occur. The system also creates awareness of other potential side effects that can occur during therapy with THALOMIDTM (thalidomide). *S.T.E.P.S.*TM requires that **all** prescribers and pharmacies register to prescribe or dispense THALOMIDTM (thalidomide) and all patients complete an informed consent process and participate in a **mandatory and confidential** surveillance registry.

Program Process

Prescriber Registration Process

All prescribers interested in treating patients with THALOMIDTM (thalidomide) must register in the THALOMIDTM (thalidomide) Prescriber Registry via a Prescriber Registration Card that is located in every *S.T.E.P.S.*TM folder.¹

Prescribers must complete, sign, and return the Prescriber Registration Card; by doing so, prescribers agree to prescribe THALOMIDTM (thalidomide) in accordance with all the terms listed on the card. Prescribers must wait for registration confirmation prior to prescribing THALOMIDTM (thalidomide).

All materials that are necessary to comply with *S.T.E.P.S.*TM program requirements are contained in the *S.T.E.P.S.*TM folder (Figure 3). The contents of **ONE FOLDER** should be used with **ONE PATIENT**, and kept with the patient's medical record. Additional *S.T.E.P.S.*TM folders can be obtained from a Celgene Immunology Specialist or by calling 1-888-4-CELGENE.

The *S.T.E.P.S.*TM folder contains the following information and materials to help ensure that fetal exposure to THALOMIDTM (thalidomide) does not occur:

Figure 3. *S.T.E.P.S.*TM materials for prescribers and patients.



- Prescriber Registration Card: **All prescribers must register.**
- Thalidomide Victims Association of Canada letter: A cautionary message to the prescriber and patient from thalidomide victims.
- *Information for Men and Women Taking THALOMID™ (thalidomide)*: This brochure should be used for patient counseling regarding the teratogenic risks as well as other side effects and precautions associated with THALOMID™ (thalidomide) therapy. A video presentation of this information will be provided to the prescriber's office upon registration.
- *Your Contraceptive Choices*: This brochure is provided to assist in counseling patients on choosing two appropriate contraceptive methods.
- *Emergency Contraception*: This brochure should be used to assist patients in the event they have unprotected heterosexual sexual intercourse while taking THALOMID™ (thalidomide).
- Patient Referral Form: A form that must be used if another health-care professional is chosen to provide contraceptive counseling for the patient.
- Patient Quiz: The quiz is provided to verify patient understanding of the risks and requirements of therapy.
- Consent Form (Figure 4): This informed consent document **must be understood and signed** before any patient can receive THALOMID™ (thalidomide).
- Thalidomide Survey Forms: These mandatory and confidential enrollment and follow-up surveys must be completed by the patient and prescriber. Men must participate, as well as women, because fetal exposure to THALOMID™ (thalidomide) could occur as a result of the presence of the drug in semen or through sharing the medication. Included are forms for patients aged 18 or older. **Forms for patients under 18 years of age are available by calling 1-888-4-CELGENE.**

Important Information for Men and Women Taking THALOMID™ (thalidomide), the Consent Form, Patient Quiz, and Survey Forms are available in 14 languages and can be obtained through a Celgene Immunology Specialist or by calling 1-888-4-CELGENE.

S.T.E.P.S.™ program requirements differ for male and female patients. Both male and female patients must receive:

- Information regarding the general guidelines for taking THALOMID™ (thalidomide).

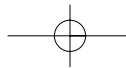
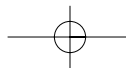


Figure 4. THALOMID™ (thalidomide) informed consent form.

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	AND	One additional effective method		
IUD		Latex condom		
Hormonal (birth control pills, injections, or implants)		Diaphragm		
Tubal ligation		Cervical cap		
Partner's vasectomy				
These birth control methods must be used for at least 4 weeks before starting THALOMID™ (thalidomide) therapy, all during THALOMID™ (thalidomide) therapy, and for at least 4 weeks after THALOMID™ (thalidomide) therapy has stopped. I must use these methods even if I am infertile, unless I have had 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 <u>completely avoid heterosexual sexual intercourse</u> . If a hormonal (birth control pills, injections, or implants) 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™ (thalidomide) therapy, then <u>every week</u> during the first 4 weeks of THALOMID™ (thalidomide) therapy. I will then have a pregnancy test <u>every 4 weeks</u> if I have regular menstrual cycles, or <u>every 2 weeks</u> if my cycles are irregular while I am taking THALOMID™ (thalidomide).			
INIT: ___ 5.	I know that I must immediately stop taking THALOMID™ (thalidomide) 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™ (thalidomide).			
INIT: ___ 7.	I understand that THALOMID™ (thalidomide) 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™ (thalidomide) 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 while taking THALOMID™ (thalidomide).			
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™ (thalidomide), which will require completing additional forms.			
CONSENT FOR MEN:				
INIT: ___ 1.	I understand that I must not take THALOMID™ (thalidomide) 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™ (thalidomide)—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™ (thalidomide) 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™ (thalidomide) 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™ (thalidomide), 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™ (thalidomide). I now authorize my doctor to begin my treatment with THALOMID™ (thalidomide).				
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™ (thalidomide) 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.)	
PRESCRIBER COPY		PRESCRIBER: PLEASE MAIL BOTTOM COPY TO SURVEY COORDINATORS		



- Comprehensive counseling on the risk of birth defects, other side effects, and important precautions associated with THALOMID™ (thalidomide) therapy as outlined in the brochure entitled *Important Information for Men and Women Taking THALOMID™ (thalidomide)* and in the informed consent form.
- **Mandatory** contraception and emergency contraception counseling.

In addition, female patients also must receive:

- Specific contraceptive counseling on the TWO methods of birth control they must use before, during, and after therapy.
- Pregnancy testing.

Pharmacy Registration Process

All retail and hospital pharmacies must be registered to dispense THALOMID™ (thalidomide). A registration card (Figure 5) outlining the terms for dispensing must be signed by the head pharmacist or director of pharmacy and returned to Celgene Corporation. When the registration information is received, the pharmacy's eligibility to dispense THALOMID™ (thalidomide) will be activated. Pharmacies must agree to:

- Refuse prescriptions written more than 7 days prior to presentation.
- Collect and retain on file a signed informed consent form with an initial prescription for THALOMID™ (thalidomide). Telephone prescriptions are not permitted.
- Register THALOMID™ (thalidomide) patients via facsimile or phone.
- Dispense blister packs intact.
- Dispense a maximum prescription of a 4-week (28-day) supply of THALOMID™ (thalidomide) therapy with no automatic refills.
- Dispense subsequent prescriptions only if fewer than 7 days of therapy remain on the previous prescription.
- Verify patient registry and record subsequent prescriptions via on-line transmission or phone.
- Educate all staff pharmacists about the dispensing procedures for THALOMID™ (thalidomide).
- Accept unused THALOMID™ (thalidomide) returned by patients.

Failure to comply with all requirements of the *S.T.E.P.S.™* program may result in the pharmacy's not being permitted to dispense THALOMID™ (thalidomide).

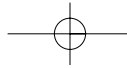


Figure 5. Pharmacy registration card.

System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.)

Pharmacy Registration

All retail and hospital pharmacies must be registered to dispense THALOMID™ (thalidomide). Please review the steps that must be followed with every patient and return this card to Celgene Corporation. Registration must be signed by the Head Pharmacist or Director of Pharmacy.

Before dispensing THALOMID™ (thalidomide), I accept responsibility to:

- Refuse prescriptions written more than 7 days prior to presentation
- Collect and file a signed informed consent form with initial prescriptions (telephone prescriptions are not permitted)
- Register patients via fax or phone
- Dispense blister packs intact
- Dispense a maximum of a 4-week (28-day) supply of THALOMID™ (thalidomide) therapy, with no automatic refills
- Dispense subsequent prescriptions only if fewer than 7 days of therapy remain on the previous prescription
- Verify patient registration and record subsequent prescriptions via on-line transmission or phone
- Educate all staff pharmacists about the dispensing procedure for THALOMID™ (thalidomide)
- Accept unused THALOMID™ (thalidomide) returned by patient

I understand that if I fail to comply with all requirements of the S.T.E.P.S. program, my pharmacy may not be permitted to dispense THALOMID™ (thalidomide).

Pharmacist Name _____ Title _____

Signature _____ Pharmacy Name _____

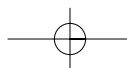
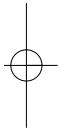
Address _____

City _____ State _____ Zip _____

Phone _____ Fax _____

Pharmacy No. _____ NABP No. _____ Preferred wholesaler _____

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Prescribing Procedures for THALOMID™ (thalidomide)

Initial Visit

When considering THALOMID™ (thalidomide) therapy for a patient, the prescriber must do the following:

- **Establish appropriateness of THALOMID™ (thalidomide) therapy versus therapeutic alternatives:**

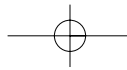
- THALOMID™ (thalidomide) is indicated for the acute treatment of the cutaneous manifestations of moderate to severe ENL. THALOMID™ (thalidomide) is not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis. THALOMID™ (thalidomide) also is indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence.

- **Provide comprehensive counseling on the risks and benefits of THALOMID™ (thalidomide) therapy:**

- Patients must be counseled on the risk of birth defects, other side effects, and important precautions associated with THALOMID™ (thalidomide) therapy.
- Men must be instructed to use a latex condom every time they have sexual intercourse with a woman, even if they have undergone a successful vasectomy.
- Utilize the patient education materials provided.

- **Determine if patient has childbearing potential:**

- If patient has undergone a hysterectomy, been postmenopausal, or had no menses for at least 24 months, continue with the instructions provided in the INITIATING THALOMID™ (thalidomide) THERAPY section.
 - **If patient is sexually mature and does not meet the above criteria, provide contraceptive counseling, including counseling on emergency contraception.**
- Female patients must thoroughly understand the need for two forms of contraception to be used AT THE SAME TIME, beginning 4 weeks before therapy, throughout therapy, and for 4 weeks after stopping therapy with THALOMID™ (thalidomide).
 - Contraceptive methods must include one highly effective method (eg, IUD, hormonal [birth control pills, injections, or implants], tubal ligation, or partner's vasectomy) and one additional effective method (eg, latex condom, diaphragm, or cervical cap).

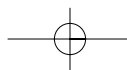


- If IUD or hormonal contraception is medically contraindicated, another highly effective method or two barrier methods must be used **AT THE SAME TIME**.
- Utilize the patient education materials provided.
 - **Prescribers may refer patients to another health-care professional for contraceptive counseling using the Patient Referral Form.**
- **Continue selected birth control options for 4 weeks prior to initiating THALOMID™ (thalidomide).**

Initiating THALOMID™ (thalidomide) Therapy

The following steps must be completed prior to initiating THALOMID™ (thalidomide) therapy¹:

- **Repeat patient counseling.**
- **Perform pregnancy test (female patients), even if continuous abstinence is the chosen method of birth control.**
 - Test must satisfy a sensitivity of least 50 mIU/mL.
 - Test must be performed on female patients of childbearing potential, **with negative results in written form**, within the 24 hours prior to initiating THALOMID™ (thalidomide) therapy.
 - Women of childbearing potential also must receive a pregnancy test every week for the first 4 weeks, then every 4 weeks thereafter if their menstrual cycles are regular.
 - If the menstrual cycle is irregular, female patients must receive a pregnancy test every 2 weeks thereafter.
 - 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 treatment, the drug must be immediately discontinued.** 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.



- **Administer the THALOMID™ (thalidomide) patient quiz.**

- Gauge patient understanding of the requirements for taking the drug.
- If the patient cannot answer all of the questions correctly, review the material that he or she does not understand.
- Readminister patient quiz. Repeat until the patient satisfactorily understands all risks and correctly answers all questions or reconsider the appropriateness of THALOMID™ (thalidomide) therapy.

- **Complete the informed consent form.**

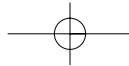
- The consent form must be read to the patient and/or parent/legal guardian in the language of his or her choice. Each statement must be initialed by the patient and/or parent/legal guardian to indicate understanding, and the form must be completed and signed by the prescriber and patient and/or parent/legal guardian.
- If the patient is under 18 years of age, his or her parent or legal guardian must read this material, sign the form, and agree to ensure compliance.
- Retain “Prescriber” copy with patient record.
- Mail “Survey Coordinators” copy (via self-mailing format).
- Instruct patient to retain “Patient” copy and to present “Pharmacist” copy with prescription to pharmacist.

- **Complete the mandatory and confidential survey enrollment form.**

- Instruct patients to complete the confidential section, seal the survey, and return it to you.
- Complete prescriber section and return survey in the envelope provided to the Slone Epidemiology Unit of Boston University School of Public Health.
- Men must complete the survey, as well as women, because failure to use a latex condom during sexual intercourse with a woman or drug-sharing could result in fetal exposure to thalidomide.

- **Provide prescription.**

- Prescriptions cannot be issued by telephone.
- Prescribe **no more than 4 weeks (28 days) of therapy**, with no automatic refills.
- Inform patients that all prescriptions must be filled within 7 days.
- It is recommended that female patients initially receive no more than a 1-week supply for each of the first 4 weeks to coincide with weekly pregnancy testing requirements.



Female Patient Monitoring During First 4 Weeks of Therapy

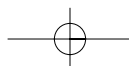
During the first 4 weeks of therapy, the following must be performed:

- **Repeat patient counseling.**
- **Perform pregnancy tests every week for the first 4 weeks of therapy.**
 - It is recommended that the tests be performed within the 24 hours before providing subsequent prescriptions.
 - Pregnancy tests must be performed even if continuous abstinence is the chosen method of birth control.
- **If pregnancy test is negative, provide prescription for a 1-week supply of THALOMID™ (thalidomide).**

Subsequent Patient Visits

On subsequent patient visits (after the first 4-week period) the following must be conducted¹:

- **Repeat patient counseling.**
- **Perform pregnancy test (female patients) every 4 weeks if patient's menstrual cycles are regular, every 2 weeks if cycles are irregular.**
 - It is recommended that the tests be performed within the 24 hours before providing subsequent prescriptions.
 - Pregnancy tests must be performed even if continuous abstinence is the chosen method of birth control.
- **If pregnancy test is negative or if the patient is male, provide prescription for no more than a 4-week (28-day) supply of THALOMID™ (thalidomide) therapy.**
- **Complete the follow-up survey form.**
 - Forms are included in the *S.T.E.P.S.*TM folder.
 - Female patients must complete the form every month. Men must complete the follow-up survey at each visit or at least every 3 months.



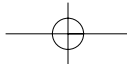
Filling a THALOMID™ (thalidomide) Prescription

The patient must present the pharmacy copy of the completed consent form along with the initial prescription to the pharmacist. The pharmacist must then:

- Ensure that the prescription was written within 7 days of presentation.
- Collect and retain the pharmacy copy of the signed informed consent form.
- Complete a patient registration form and enroll the patient in the *S.T.E.P.S.™* Patient Registry by telephone or facsimile.
- Dispense blister packs intact.
- Dispense no more than a 4-week (28-day) supply of THALOMID™ (thalidomide), with no automatic refills.

When subsequent prescriptions are presented to the pharmacy, the pharmacist must:

- Ensure that the prescription was written within 7 days of presentation.
- Verify patient registration and record subsequent prescriptions in the THALOMID™ (thalidomide) Patient Registry via on-line transmission or telephone.
- Ensure that fewer than 7 days remain on the previous prescription.
- Dispense blister packs intact.
- Dispense no more than a 28-day supply of THALOMID™ (thalidomide).



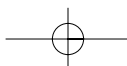
HOW SUPPLIED AND DISPENSED

THALOMID™ (thalidomide) is supplied in 50-mg white, opaque, hard gelatin capsules imprinted with “Celgene” and a “DO NOT GET PREGNANT” logo.¹ Boxes contain six blister packages containing 14 capsules each (84 capsules total).¹

THALOMID™ (thalidomide) should be dispensed in no more than a 1-month supply and only on presentation of a new prescription written within the previous 7 days.¹ Informed consent and compliance with the mandatory patient registry and survey are required for both men and women prior to dispensing.¹ THALOMID™ (thalidomide) prescribing to women of childbearing potential should be contingent upon initial and continued confirmed negative results of pregnancy testing.¹ Prescriptions cannot be telephoned to the pharmacy.

THALOMID™ (thalidomide) must not be repackaged.¹ Packages of THALOMID™ (thalidomide) should be stored at 59 °F to 86 °F (15 °C to 30 °C) and protected from light.¹

Further information about THALOMID™ (thalidomide) and *S.T.E.P.S.*™ can be obtained by calling Celgene Corporation at 1-888-4-CELGENE.



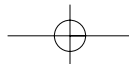
THALOMID™ (thalidomide): BALANCING THE BENEFITS AND THE RISKS

ENL develops in some patients with Hansen's disease, usually after they have been in treatment for a period of time. ENL is not a reaction to drugs or treatment but a reaction of the immune system to dead mycobacteria that remain in the body. Patients with this condition may be acutely ill with fever, painful eruptions in the skin, joint pain, and nerve pain in the extremities. During this reaction, nerve damage to the hands, feet, and eyes can occur. If left untreated, individual episodes will last for several weeks and tend to recur for many months and sometimes for several years.

Prednisone or other corticosteroids are effective in controlling ENL, but their long-term use results in side effects such as weight gain, diabetes, hypertension, cataracts, and osteoporosis with collapsed vertebrae of the spine. These side effects can be serious and permanent. Clofazimine is of some benefit in the treatment of ENL, but it is slow-acting and causes skin pigmentation. In most patients, THALOMID™ (thalidomide) can control the cutaneous manifestations of moderate to severe ENL.

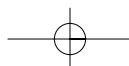
Thalidomide has the potential to cause significant adverse effects. However, these can be avoided or managed if it is prescribed appropriately. The most serious and well-known adverse effect of thalidomide is severe birth defects when it is administered during early stages of pregnancy. Therefore, thalidomide must be prescribed and dispensed in accordance with mandatory guidelines designed to help ensure that fetal exposure to the drug does not occur.

Thalidomide has been used for more than 25 years in the United States and other countries for the treatment of ENL and has proved very useful for managing this difficult chronic problem without the long-term use of corticosteroids and their associated side effects. There have been no known cases of birth defects in the United States resulting from the use of thalidomide for ENL, although some have occurred in other countries where controls and monitoring plans have been inadequate. Thalidomide must be administered under appropriately supervised and controlled conditions. It is critical that prescribers, pharmacists, and patients be adequately informed about the teratogenic risk and other potential adverse effects that occur in both men and women.



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THALOMID™ (thalidomide)

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™ (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.™)".

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), hypoplasia of the bones, absence of bones, external ear abnormalities (including anopia, micro pima, 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 (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

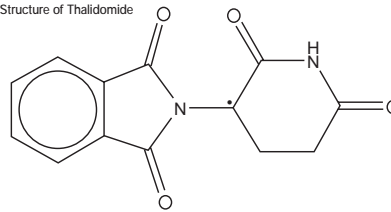
Thalidomide is contraindicated in sexually mature MALES unless the PATIENT MEETS ALL OF THE FOLLOWING CONDITIONS:

- 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-phthalimidoglutarimide), is an immunomodulatory agent. The empirical formula for thalidomide is C₁₇H₁₅N₃O, 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- α (TNF- α) production and down-modulation of selected cell surface adhesion molecules involved in leukocyte migration^{1,4,5}. For example, administration of thalidomide has been reported to decrease circulating levels of TNF- α in patients with ENL⁴, however, it has also been shown to increase plasma TNF- α levels in HIV-seropositive patients⁷.

Pharmacokinetics and Drug Metabolism

Absorption

The absolute bioavailability of thalidomide from THALOMID™ (thalidomide) 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™ (thalidomide) ranged from 2.9 to 5.7 hours indicating that THALOMID™ (thalidomide) is slowly absorbed from the gastrointestinal tract. While the extent of absorption (as measured by area under the curve [AUC]) is proportional to dose in healthy subjects, the observed peak concentration (C_{max}) increased in a less than proportional manner (see Table 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™ (thalidomide) 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™ (thalidomide). 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 <i>et al</i> ³ Bull World Health Organization 1971; 45:719	92	204	Thalidomide 75%	Aspirin 25%
Sheskin <i>et al</i> ²⁶ 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)

Waters²¹ 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 ²¹ Lep Rev 1971; 42:26	4 weeks	9	4/5	0/4
	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 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.

INDICATIONS AND USAGE

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

THALOMIDTM (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.

THALOMIDTM (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 WARNINGS** 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/mm³. 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/mm³ 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 log₁₀ 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-seropositive²². The clinical significance of this increase is unknown. Both studies were conducted prior to availability of highly active anti-retroviral 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 THALOMIDTM (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, THALOMIDTM (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 presently unknown.

Information for Patients (See BOXED WARNINGS.)

Patients 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.TM 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.TM 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 (ASS2 Chinese hamster ovary cells; ASS2/XPR1 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 counseling. Any suspected fetal exposure to THALOMIDTM (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 of 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 investigational 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™ (thalidomide)-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™ (thalidomide)-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	AEs Reported in ≥ 3 HIV-seropositive Patients			
	All AEs Reported in ENL Patients 50 to 300 mg/day (N=24)	Thalidomide 100 mg/day (N=36)	Thalidomide 200 mg/day (N=32)	Placebo (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 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. 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™ (thalidomide) 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™ (thalidomide) 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, 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, hypercholesterolemia, 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.

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, gynecostasia, hangover effect, hypomagnesemia, hypothyroidism, lymphedema, lymphopenia, metrorrhagia, migraine, myxedema, nodular sclerosing Hodgkin's disease, nyctagmus, 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.

DOSEAGE 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.

For an episode of cutaneous ENL, THALOMID™ (thalidomide) 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™ (thalidomide) 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™ (thalidomide). Steroid usage can be tapered and discontinued when the neuritis has ameliorated.

Dosing with THALOMID™ (thalidomide) 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 of 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)
59572-105-11

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 7 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 for 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	AND	One additional effective method
IUD		Latex condom
Hormonal (birth control pills, injections, or implants)		Diaphragm
Tubal ligation		Cervical cap
Partner's vasectomy		

These birth control methods must be used for at least 4 weeks before starting THALOMID™ (thalidomide) therapy, all during THALOMID™ (thalidomide) therapy, and for at least 4 weeks after THALOMID™ (thalidomide) therapy has stopped. I must use these methods even if I am infertile, unless I have had 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, injections, or implants) 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™ (thalidomide) therapy, then every week during the first 4 weeks of THALOMID™ (thalidomide) 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™ (thalidomide).

INIT. ___ 5. I know that I must immediately stop taking THALOMID™ (thalidomide) 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™ (thalidomide).

INIT. ___ 7. I understand that THALOMID™ (thalidomide) 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™ (thalidomide) 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 while taking THALOMID™ (thalidomide).

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™ (thalidomide), which will require completing additional forms.

CONSENT FOR MEN:

INIT. ___ 1. I understand that I must not take THALOMID™ (thalidomide) 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™ (thalidomide)-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™ (thalidomide) 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™ (thalidomide) 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™ (thalidomide), 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™ (thalidomide). I now authorize my doctor to begin my treatment with THALOMID™ (thalidomide).

Patient Name (please print)	Social Security No. (Only last six digits required)	Date of Birth (mo./day/yr)
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Patient, Parent/Guardian Signature	Date (mo./day/yr)
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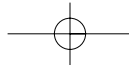
I have fully explained to the patient the nature, purpose, and risks of the treatment described above, especially the risks to women of childbearing potential. I have asked the patient if she/he has any questions regarding her/his treatment with THALOMID™ (thalidomide) and have answered those questions 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.
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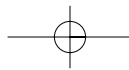
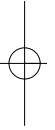
Physician Signature	Date (mo./day/yr)
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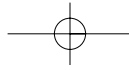
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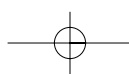
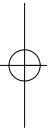
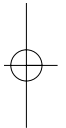


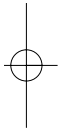
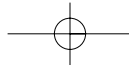
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Celgene Corporation
Warren, NJ 07059 USA

