CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-785 / S-020, S-021

Trade Name: THALOMID

Generic Name: (Thalidomide)

Sponsor: Celegene Corporation

Approval Date: January 17, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-785 / S-020, S-021

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-785 / S-020, S-021

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-785/S-020 and S-021

Celgene Corporation
Attention: Steve Thomas, Ph.D.
Vice President, Project Management and Regulatory Affairs
7 Powder Horn Drive
Warren, NJ 07059

Dear Dr. Thomas:

Please refer to your supplemental new drug application (S-020) dated and received March 1, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Thalomid® (thalidomide) Capsules.

This supplemental new drug application (S-020) provides for the following:

- A change to a higher potency blend formulation, replacement of the current marketed 50-mg capsule with a new 50-mg capsule formulation, and the introduction of a 100-mg and a 200-mg capsule.
- Revised cartons, blister pack cards, and package insert (**DESCRIPTION** and **HOW SUPPLIED** sections) to reflect the new formulation and addition of the 100-mg and 200-mg capsules.

Please also refer to your supplemental new drug application (S-021) dated and received May 24, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Thalomid® (thalidomide) Capsules.

This supplemental new drug application (S-021) provides for the following:

- Changes to the labeling to comply with Enhanced S.T.E.P.S. (System for Thalidomide Education and Prescribing Safety).
- Revised cartons, blister pack cards, and package insert to reflect additional labeling revisions for the new formulation and addition of the 100-mg and 200-mg capsules.

We acknowledge receipt of your submissions dated December 6, December 10, December 19, and December 20, 2002 as well as January 3 and January 9, 2003.

Your submission of January 16, 2003, constituted a complete response to our December 6, 2002 action letter.

We have completed the review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (package insert submitted May 24, 2002) and to the submitted labeling (carton labels submitted January 3, 2003, and blister pack labels submitted January 16, 2003).

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please mount individually ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDAs (January 1999). For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 20-785/S-020 and NDA 20-785/S-021." Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Matthew A. Bacho, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and
Immunologic Drug Products
Office of Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Renata Albrecht
1/17/03 03:59:16 PM
NDA 20-785/S-020 and S-021

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-785 / S-020, S-021

APPROVED LABELING

THALOMID® (thalidomide) Capsules 50 mg, 100 mg, & 200 mg

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, 100 mg or 200 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), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia, micro pinna, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented.[1] Mortality at or shortly after birth has been reported at about 40%.[2]

Effective contraception (see **CONTRAINDICATIONS**) must be used for at least 4 weeks before beginning thalidomide therapy, during thalidomide therapy, and for 4 weeks 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 postmenopausal for at least 24 months. Two reliable forms of contraception must be used simultaneously unless continuous abstinence from heterosexual sexual contact 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 postmenopausal for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months) are considered to be women of childbearing potential.

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

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

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

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

Any suspected fetal exposure to THALOMID® (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 heterosexual sexual contact is the chosen method. (Sexually mature women who have not undergone a hysterectomy or who have not been postmenopausal for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months) are considered to be women of childbearing potential.)
- she acknowledges, in writing, her understanding of these warnings and of the need for using two reliable methods of contraception for 4 weeks prior to ~~starting~~ beginning thalidomide therapy, during thalidomide therapy, and for 4 weeks after ~~stopping~~ discontinuation of thalidomide therapy.
- she has had a negative pregnancy test with a sensitivity of at least 50 mIU/mL, within the 24 hours prior to beginning therapy. (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

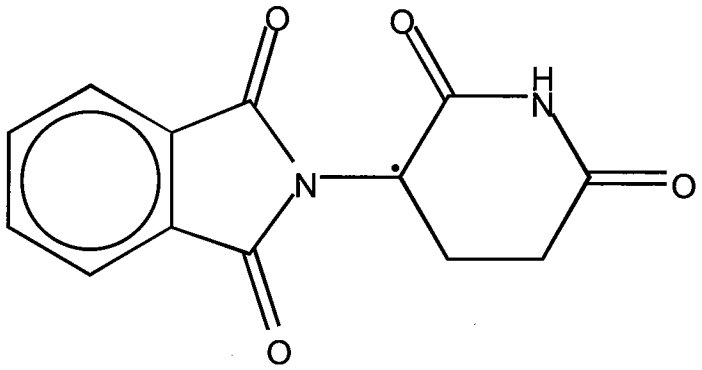
Thalidomide is contraindicated in sexually mature MALES unless the PATIENT MEETS ALL OF THE FOLLOWING CONDITIONS:

- 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 presence of thalidomide in semen. He has been instructed that he must always use ~~barrier contraception~~ a ~~(~~latex condom~~)~~ during any sexual contact with women of childbearing potential, even if he has undergone a successful vasectomy.
- he acknowledges, in writing, his understanding of these warnings and of the need to use ~~barrier contraception~~ a ~~(~~latex condom~~)~~ during any sexual contact with women of childbearing potential, even if he has undergone a successful vasectomy. Sexually mature women who have not undergone a hysterectomy or who have not been postmenopausal for at least 24 consecutive months (i.e., who have had menses at any time in the preceding 24 consecutive months) are considered to be women of childbearing potential.
- if the patient is between 12 and 18 years of age, his parent or legal guardian must have read this material and agreed to ensure compliance with the above.

DESCRIPTION

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

Chemical Structure of thalidomide



Note:•=asymmetric carbon atom

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

THALOMID® (thalidomide) is available in 50 mg, 100 mg and 200 mg capsules for oral administration. Active ingredient: thalidomide. Inactive ingredients: ~~anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.~~ pregelatinized starch and magnesium stearate. The 50 mg capsule shell contains gelatin, titanium dioxide, and black ink. The 100 mg capsule shell contains black iron oxide, yellow iron oxide, titanium dioxide, gelatin, and black ink. The 200 mg capsule shell contains FD&C blue #2, titanium dioxide, gelatin, and white ink.

CLINICAL PHARMACOLOGY

Mechanism of Action

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

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

Pharmacokinetics and Drug Metabolism

Absorption

The absolute bioavailability of thalidomide from THALOMID® (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	$AUC_{0\infty}$ 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%)

Coadministration 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
In human blood plasma, the geometric mean plasma protein binding was 55% and 66%, respectively, for (+)-(R)- and (-)-(S)-thalidomide.[8] In a pharmacokinetic study of thalidomide in HIV-seropositive adult male subjects receiving thalidomide 100 mg/day, thalidomide was detectable in the semen.

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,[9] 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 *et al.*[10] Bull World Health Organization 1971;45:719	92	204	Thalidomide 75%	Aspirin 25%
Sheskin *et al.*[11] Int J Lep 1969;37:135	52	173	Thalidomide 66%	Placebo 10%

*In patients with cutaneous lesions

**Iyer: Complete response or lesions absent

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

Waters[12] 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[12] 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

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

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

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

CONTRAINDICATIONS (See BOXED WARNINGS.)

Pregnancy: Category X

Due to its known human teratogenicity, even following a single dose, thalidomide is contraindicated in pregnant women and women capable of becoming pregnant. (See **BOXED WARNINGS**.) When there is no alternative treatment, women of childbearing potential may be treated with thalidomide provided adequate precautions are taken to avoid pregnancy. Women must commit either to abstain continuously from heterosexual sexual contact 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~~ Drug Interactions**), two other effective or highly effective methods may be used.

Women of childbearing potential being treated with thalidomide should have a pregnancy test~~ing~~ (sensitivity of at least 50 mIU/mL). The test should be performed within the 24 hours ~~before~~ prior to beginning thalidomide therapy and then weekly during the first ~~month~~ 4 weeks of thalidomide therapy, then ~~month thereafter~~ at 4 week intervals in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding. If pregnancy occurs during thalidomide treatment, thalidomide must be ~~immediately~~ discontinued immediately. Under these conditions, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

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

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

WARNINGS (See BOXED WARNINGS.)

Birth Defects ~~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 thalidomide is present in the semen of patients receiving the drug, males receiving thalidomide must always use a latex condom during any sexual contact with women of childbearing potential.

Drowsiness and Somnolence ~~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 ~~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 ~~orthostatic hypotension~~:
Patients should also be advised that thalidomide may cause dizziness and orthostatic hypotension and that, therefore, they should sit upright for a few minutes prior to standing up from a recumbent position.

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

Increased HIV Viral ~~HIV-Viral~~ Load:
In a randomized, placebo controlled trial of thalidomide in an HIV-seropositive patient population, plasma HIV RNA levels were found to increase (median change = 0.42 $\log_{10}$ copies HIV RNA/mL, p = 0.04 compared to placebo). [7] A similar trend was observed in a second, unpublished study conducted in patients who were HIV- seropositive[~~13~~13]. The clinical

significance of this increase is unknown. Both studies were conducted prior to availability of highly active antiretroviral therapy. Until the clinical significance of this finding is further understood, in HIV-seropositive patients, viral load should be measured after the first and third months of treatment and every 3 months thereafter.

PRECAUTIONS

Hypersensitivity:
Hypersensitivity to THALOMID® (thalidomide) has been reported. Signs and symptoms have included the occurrence of erythematous macular rash, possibly associated with fever, tachycardia, and hypotension, and if severe, may necessitate interruption of therapy. If the reaction recurs when dosing is resumed, THALOMID® (thalidomide) should be discontinued.

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

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

Seizures:
Although not reported from pre-marketing controlled clinical trials, seizures, including grand mal convulsions, have been reported during post-approval use of THALOMID® (thalidomide) in clinical practice. Because these events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. Most patients had disorders that may have predisposed them to seizure activity, and it is not currently known whether thalidomide has any epileptogenic influence. During therapy with thalidomide, patients with a history of seizures or with other risk factors for the development of seizures should be monitored closely for clinical changes that could precipitate acute seizure activity.

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.*® program and boxed warnings in this package insert. Patients should be instructed to take thalidomide only as prescribed in compliance with all of the provisions of the *S.T.E.P.S.*® Restricted Distribution Program.

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

Patients should be instructed that thalidomide frequently causes drowsiness and somnolence. Patients should be instructed to avoid situations where drowsiness may be a problem and not to take other medications that may cause drowsiness without adequate medical advice. Patients should be advised as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks, such as driving a car or operating other complex machinery. Patients should be instructed that thalidomide may potentiate the somnolence caused by alcohol.

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

Patients should also be instructed that thalidomide may cause dizziness and orthostatic hypotension and that, therefore, they should sit upright for a few minutes prior to standing up from a recumbent position.

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

Laboratory Tests

Pregnancy Testing: **(See BOXED WARNINGS.)** Women of childbearing potential should have a pregnancy test 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~~ 4 weeks of use, then at 4 week intervals in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Pregnancy testing and counseling should ~~also~~ be performed if a patient misses her period or if there is any abnormality in menstrual bleeding.

Neutropenia: **(See WARNINGS.)**

Increased 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 heterosexual sexual contact.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

Pregnancy

Pregnancy Category X: **(See BOXED WARNING and CONTRAINDICATIONS.)**
Because of the known human teratogenicity of thalidomide, thalidomide is contraindicated in women who are or may become pregnant and who are not using the two required types of birth control or who are not continually abstaining from heterosexual sexual contact. 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, 100 mg, or a 200 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 THALOMID® (thalidomide) must be reported to the FDA *via* the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation.

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

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

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

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

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

ADVERSE REACTIONS
The most serious toxicity associated with thalidomide is its documented human teratogenicity. (See **BOXED WARNINGS** and **CONTRAINDICATIONS.**) The risk of severe birth defects, primarily phocomelia or death to the fetus, is extremely high during the critical period of pregnancy. The critical period is estimated, depending on the source of information, to range from 35 to 50 days after the last menstrual period. The risk of other potentially severe birth defects outside this critical period is unknown, but may be significant. Based on present knowledge, thalidomide must not be used at any time during pregnancy.

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

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

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

Somnolence, dizziness, and rash are the most commonly observed adverse events associated with the use of thalidomide. Thalidomide has been studied in controlled and uncontrolled clinical trials in patients with ENL and in people who are HIV-seropositive. In addition, thalidomide has been administered investigationally for more than 20 years in numerous indications. Adverse event profiles from these uses are summarized in the sections that follow.

Other Adverse Events

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

Incidence in Controlled Clinical Trials

Table 4 lists treatment-emergent signs and symptoms that occurred in THALOMID® (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~~ three 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	All AEs Reported in ENL Patients 50 to 300 mg/day (N=24)	AEs Reported in ≥3 HIV-seropositive Patients 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 investigationally in the United States over a 19-year period in 1465 patients with ENL. The published literature describes the treatment of an additional 1678 patients. To provide a meaningful estimate of the proportion of the individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using a modified COSTART dictionary/terminology. These categories are used in the listing below. All reported events are included except those already listed in the previous table. Due to the fact that these data were collected from uncontrolled studies, the incidence rate cannot be determined. As mentioned previously, **no causal relationship between thalidomide and these events can be conclusively determined at this time**. These are reports of all adverse events noted by investigators in patients to whom they had administered thalidomide.

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

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

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

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

Metabolic and Endocrine: ADH inappropriate, 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, hypercholesteremia, hypoglycemia, increased alkaline phosphatase, increased lipase, increased serum creatinine, peripheral edema.

Muscular Skeletal: Myalgia, myasthenia.

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

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

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

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

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

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

DRUG ABUSE AND DEPENDENCE

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

THALOMID® (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 off medication should be attempted every 3 to 6 months, in decrements of 50 mg every 2 to 4 weeks.

HOW SUPPLIED

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

THALOMID® (thalidomide) ~~is~~ Capsules are supplied in the following dosages:

~~hard gelatin,~~ 50 mg capsules [white opaque], imprinted "Celgene / 50 mg" with a "Do Not Get Pregnant" logo.

Individual blister packs of 28 capsules (NDC 59572-XXX-XX).

Boxes of 140 containing 10 prescription packs of 14 capsules each (NDC 59572-105-92).
Boxes of 280 containing 10 prescription packs of 28 capsules each (NDC ~~59572-105-93~~ 59572-XXX-XX).

100 mg capsules [tan], imprinted "Celgene / 100 mg" with a "Do Not Get Pregnant" logo.

Individual blister packs of 28 capsules (NDC 59572-XXX-XX).
Boxes of 140 containing 5 prescription packs of 28 capsules each (NDC 59572-XXX-XX).

200 mg capsules [blue], imprinted "Celgene / 200 mg" with a "Do Not Get Pregnant" logo.

Individual blister packs of 28 capsules (NDC 59572-XXX-XX).

Boxes of 84 containing 3 prescription packs of 28 capsules each (NDC 59572-XXX-XX).

STORAGE AND DISPENSING

PHARMACISTS NOTE:

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

This drug must not be repackaged.

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

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

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

1-(888) 423-5436

Important Information and Warnings for All Patients Taking 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, 100 mg or 200 mg)] TAKEN BY A PREGNANT WOMAN CAN CAUSE SEVERE BIRTH DEFECTS.

All Patients

- The patient understands that severe birth defects can occur with the use of THALOMID® (thalidomide).
- The patient has been warned by his/her doctor that an unborn baby will almost certainly have ~~serious~~ severe birth defects and can even die, if a woman is pregnant or becomes pregnant while taking THALOMID® (thalidomide).
- THALOMID® (thalidomide) will be prescribed ONLY for the patient and must NOT be shared with ANYONE, even someone who has similar symptoms.

- THALOMID® (thalidomide) must be kept out of the reach of children and should NEVER be given to women who are able to have children.
- The patient cannot donate blood while taking THALOMID® (thalidomide).
- The patient has read the THALOMID® (thalidomide) patient brochure and/or viewed the videotape, "Important Information for Men and Women Taking THALOMID® (thalidomide)" and understands the contents, including other possible health problems from THALOMID® (thalidomide), "side effects."
- The patient's doctor has answered any questions the patient has asked.
- The patient must participate in a telephone survey and patient registry, while taking THALOMID® (thalidomide).

Female Patients of Childbearing Potential

- The patient must not take THALOMID® (thalidomide) if she is pregnant, breast-feeding a baby, or able to get pregnant and not using the required two methods of birth control.
- The patient confirms that she is not now pregnant, nor will she try to become pregnant during THALOMID® (thalidomide) therapy and for at least 4 weeks after she has completely finished taking THALOMID® (thalidomide).
- If the patient is able to become pregnant, she 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~~ beginning THALOMID® (thalidomide) therapy, ~~all~~ during THALOMID® (thalidomide) therapy, and for 4 weeks ~~after~~ following discontinuation of THALOMID® (thalidomide) therapy ~~has stopped~~.
- The patient must use these birth control methods unless she completely abstains from heterosexual sexual contact.
- If a hormonal method (birth control pills, injections, or implants) or IUD is not medically possible for the patient, she may use another highly effective method or two barrier methods AT THE SAME TIME.
- The patient must have a pregnancy test done by her doctor within the 24 hours prior to starting THALOMID® (thalidomide) therapy, then every week during the first 4 weeks of THALOMID®(thalidomide) therapy.
- Thereafter, the patient must have a pregnancy test every 4 weeks if she has regular menstrual cycles, or every 2 weeks if her cycles are irregular while she is taking THALOMID® (thalidomide).
- The patient must immediately stop taking THALOMID® (thalidomide) and inform her doctor:
  - If she becomes pregnant while taking the drug
  - If she misses her menstrual period, or experiences unusual menstrual bleeding
  - If she stops using birth control
  - If she thinks FOR ANY REASON that she may be pregnant

  The patient understands that if her doctor is not available, she can call 1-888-668-2528 for information on emergency contraception.

Female Patients Not of Childbearing Potential

- The patient certifies that she is not now pregnant, nor of childbearing potential as she has been postmenopausal for at least 24 months (been through the change of life); or she has had a hysterectomy.
- The patient or guardian certifies that a prepubertal female child is not now pregnant, nor is of childbearing potential as menstruation has not yet begun, and/or the child will not be engaging in heterosexual sexual contact for at least 4 weeks before THALOMID® (thalidomide) therapy, during THALOMID® (thalidomide) therapy, and for at least 4 weeks after stopping therapy.

Male Patients

- The patient has been told by his doctor that he must NEVER have unprotected sexual contact with a woman who can become pregnant.
- Because THALOMID® (thalidomide) is present in semen, his doctor has explained that he must either completely abstain from sexual contact with women who are pregnant or able to become pregnant, or he must use a latex condom EVERY TIME he engages in any sexual contact with women who are pregnant or may become pregnant while he is taking THALOMID® (thalidomide) and for 4 weeks after he stops taking the drug, even if he has had a successful vasectomy.
- The patient must inform his doctor:
  If he has had unprotected sexual contact with a woman who can become pregnant
  If he thinks FOR ANY REASON, that his sexual partner may be pregnant.
  The patient understands that if his doctor is not available, he can call 1-888-668-2528 for information on emergency contraception.
- The patient cannot donate semen or sperm while taking THALOMID® (thalidomide).

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 Signature_____Date_____

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 he/she has any questions regarding his/her treatment with THALOMID® (thalidomide) and have answered those questions to the best of my ability. I will comply with all of my obligations and responsibilities as a prescriber registered under the *S.T.E.P.S.*® restricted distribution program.

Prescriber Name (please type): _____

DEA Number:_____ Social Security Number if PA or NP: _____

Street Address: _____

City: _____ State: _____ Zip: _____

Prescriber Signature _____

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~~THALPI.005 8/01 CG~~ S.T.E.P.S.® is a registered trademark of Celgene Corporation.
U.S. Pat. Nos. 6,045,501 & 6,315,720.
THALPI.006 XX/XX CG

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-785 / S-020, S-021

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-785/S-020

Celgene Corporation
Attention: Steve Thomas, Ph.D.
Vice President, Management and Regulatory Affairs
7 Powder Horn Drive
Warren, NJ 07059

Dear Dr. Thomas:

Please refer to your supplemental new drug application dated and received March 1, 2002, which was submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Thalomid® (thalidomide) Capsules.

We acknowledge receipt of your submissions dated April 5 and May 8, 2002.

This supplemental new drug application provides for new 50, 100, and 200-mg strengths of Thalomid® Capsules.

We have completed the review of this supplemental application and it is approvable. Before this supplement may be approved, however, it will be necessary for you to:

1. Conduct dissolution testing using [redacted] at [redacted] at the three new strengths of thalidomide and compare them to the approved 50-mg capsule. The test should be conducted on 12 units of thalidomide capsules for each thalidomide dosage strength.
2. Provide individual and mean dissolution data and profiles comparing the 50, 100, and 200-mg capsules to the approved 50-mg capsule using the proposed method [redacted] and also using [redacted]
3. Provide individual and mean dissolution data and profiles comparing the 100-mg to the approved 50-mg capsule using an appropriate and acceptable media, which would facilitate our consideration of the waiver of a bioequivalence study comparing the two strengths. The dissolution test should be conducted with 12 units of each approved 50-mg capsule and the proposed 100-mg capsule. In addition, you should compute the similarity factor (f_2) comparing the dissolution profiles requested.
4. Indicate whether the new 100- and 200-mg products pass the current NDA/USP dissolution test and provide dissolution profiles for all strengths of the new formulation using the current compendial monograph method. Data indicate that the new 50-mg capsule formulation meets the current NDA (and USP) dissolution test (see p. 040270, for example). On the same page it is stated that the current dissolution method "was

developed for the old formulation of 50 mg capsules only" and "is not applicable to the new higher strengths." Please note, however, that the dissolution method developed by the FDA's Division of Drug Analysis (i.e., the current regulatory method) was routinely used to characterize earlier investigational 100-mg formulations, including earlier Celgene product. If product does not comply with the current USP dissolution test, the product must be labeled accordingly.

5. Submit the physical characteristics (particle size distribution, BET surface area) of [redacted] (see comparative dissolution study on p. 040712).
6. Revise the Stability Matrix, First Three Commercial Batches (p. 038489) to include testing of all batches at the expiry.
7. Submit the Certificate of Analysis and dissolution profiles of current formulation lot 0403S used in the bioequivalence studies.

Within 10 days after the date of this letter, you are required to amend this supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may proceed to withdraw this supplemental application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change prior to approval of this supplemental application.

If you have any questions, call Matthew A. Bacho, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Acting Director
Division of Special Pathogen and
Immunologic Drug Products
Office of Evaluation IV
Center for Drug Evaluation and Research

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/s/

Renata Albrecht
7/1/02 04:49:24 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-785/S-020 and S-021

Celgene Corporation
Attention: Steve Thomas, Ph.D.
Vice President, Project Management and Regulatory Affairs
7 Powder Horn Drive
Warren, NJ 07059

Dear Dr. Thomas:

Please refer to your supplemental new drug application (S-020) dated and received March 1, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Thalomid® (thalidomide) Capsules.

We acknowledge receipt of your submissions dated April 5, May 8, July 3, July 9, and December 5, 2002.

Your submission of August 7, 2002, constituted a complete response to our July 1, 2002 action letter.

This supplemental new drug application (S-020) provides for the following:

- A change to a higher potency blend formulation, replacement of the current marketed 50-mg capsule with a new 50-mg capsule formulation, and the introduction of a 100-mg and a 200-mg capsule.
- Revised cartons, blister pack cards, and package insert (**DESCRIPTION** and **HOW SUPPLIED** sections) to reflect the new formulation and addition of the 100-mg and 200-mg capsules.

Please also refer to your supplemental new drug application (S-021) dated and received May 24, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Thalomid® (thalidomide) Capsules.

We acknowledge receipt of your submissions dated May 30, August 26, September 13, and November 19, 2002.

This supplemental new drug application (S-021) provides for the following:

- Changes to the labeling to comply with Enhanced S.T.E.P.S. (System for Thalidomide Education and Prescribing Safety).

- Revised cartons, blister pack cards, and package insert to reflect additional labeling revisions for the new formulation and addition of the 100-mg and 200-mg capsules.

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit draft printed labeling revised as follows:

Carton Labeling (50 mg, 100 mg, and 200 mg)

- Please relocate the net quantity to the bottom of the carton labeling in order to prevent confusion with the dosage strength.
- In order to prevent medication errors, please increase the prominence of the dosage strength and assure adequate contrast between the dosage strength and the background.
- The statement, "Dispense no more than a 4-week (28-day) supply, with no automatic refills," is unclear. Please revise the statement to read, "Dispense no more than a 4-week (28-day) supply. A prescription for Thalomid is NOT refillable."
- The statement, "Dispense Blister Packs Intact," appears only on the outer shipping carton. The placement of this statement did not prevent an incident where the Thalomid® blister pack was cut apart, leaving the Thalomid® capsules unidentified. Please include this statement on the carton.

Blister Pack Labels (50 mg, 100 mg, and 200 mg)

- Please apply the first two bullets from Carton Labeling above to the blister pack labels.
- Currently, Thalomid® is available in blister packs of 14 and 28 capsules; unit doses are not available for inpatient settings. We received a medication error report from a hospital where a Thalomid® blister pack had been cut apart into individual doses, leaving the separated capsules without any identification. Please revise the blister packaging so that the proprietary and established names, product strength, lot number, and expiration date appear on the foil backing of each Thalomid® capsule. The "Do-Not-Get-Pregnant" logo should be retained for each capsule.
- Please include the statement, "Dispense Blister Packs Intact," on the blister card as well.

In addition, all previous revisions as reflected in the most recently approved package insert must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, as required by 21 CFR 314.550, submit three copies of all promotional materials including promotional labeling and advertisements that you intend to use within 120 days following approval of this product. Submit all proposed materials in draft or mock up form, not final print. Send one copy to this division and two copies of both the promotional materials and the proposed package insert directly to:

Division of Drug Marketing, Advertising
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857

Within 10 days after the date of this letter, you are required to amend these applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may proceed to withdraw these applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of these supplemental applications.

If you have any questions, call Matthew A. Bacho, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and
Immunologic Drug Products
Office of Evaluation IV
Center for Drug Evaluation and Research

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/s/

Renata Albrecht
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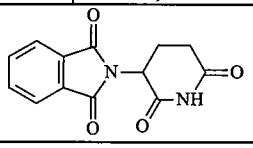
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-785 / S-020, S-021

CHEMISTRY REVIEW(S)

SUPPLEMENTAL NDA CHEMIST'S REVIEW	1. ORGANIZATION HFD-590	2. NDA NUMBER 20-785
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Celgene Corporation 7 Powder Horn Drive Warren, New Jersey 07059		4. SUBMISSION TYPE: PA 5. DOCUMENT(S) NUMBER(S) SCF-020 DATE(S) 2/1/02
6. NAME OF DRUG Thalomid	7. NONPROPRIETARY NAME thalidomide	
8. SUPPLEMENT(S) PROVIDES FOR: a new formulation and new strengths for Thalomid (thalidomide) Capsules.		9. AMENDMENTS AND OTHER *(Reports, etc.)* DATES BC 4/5/02, 5/8/02
10. PHARMACOLOGICAL CATEGORY Immunomodulator	11. HOW DISPENSED |X| Rx | | OTC	12. RELATED IND/NDA/DMF(S)
13. DOSAGE FORM(S) Capsule	14. POTENCY(IES) 50-, 100- and 200-mg	
15. CHEMICAL NAME/STRUCTURE (1) N-(2,6-dioxo-3-piperidyl)phthalimide (2) α-(N-phthalimido)glutarimide		16. MEMORANDA Telephone conversations: 5/3/02 and 5/6/02

17. COMMENTS

The current commercial product consists of a 50-mg capsule approved on July 16, 1998. This supplement describes a reformulated product to be available in 50-, 100- and 200-mg strengths. The three strengths are manufactured from a common —— thalidomide blend. ——

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The same manufacturing, packaging and testing facilities currently approved under NDA 20-785 will be used. The container/closure system consists of a blister package similar to that used with the approved product. Tests for appearance, identification, assay, related substances and content uniformity are also the same as approved for the current 50-mg capsule. Celgene has proposed a new dissolution method that uses a standard ' ——

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——

It is not clear if the new strengths of the reformulated product will pass the current USP thalidomide capsule monograph dissolution test. If not, they will need to be labeled accordingly. Additional dissolution tests evaluating and paddle speed across all capsule strengths are needed to justify the proposed dissolution method. The proposed 36-month expiration dating period is acceptable.

The *in vivo* bioequivalence studies submitted in support of the new formulation and strengths, and *in vitro* dissolution data, have been reviewed by Dr. K. Kumi, Biopharmaceutics Reviewer. Bioequivalence of the new 50-mg capsule and the current 50-mg capsule and bioequivalence of the new 50-mg product and the new 200-mg capsule have been demonstrated. However, several issues related to the dissolution test were identified in his review.

18. CONCLUSIONS AND RECOMMENDATIONS

The composition and manufacture of the new formulation and strengths of thalidomide capsules are adequately documented. With the exception of the dissolution test, the proposed controls are the same as approved for the current 50-mg formulation. From the chemist's perspective this supplement is approvable pending resolution of outstanding issues related to the dissolution method and acceptance criteria identified in this review and by Dr. Kumi.

19. REVIEWER	SIGNATURE	DATE COMPLETED
Mark R. Seggel	{See appended electronic signature page}	June 26, 2002

20. CONCURRENCE: HFD-590/NSchmuff {See appended electronic signature page}

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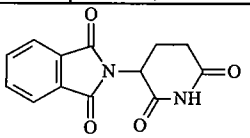
/s/

Matthew Bacho
7/1/02 04:56:44 PM
CSO

Gene Holbert
7/1/02 05:03:07 PM
CHEMIST

SUPPLEMENTAL NDA CHEMISTRY REVIEW #2	1. ORGANIZATION HFD-590	2. NDA NUMBER 20-785
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Celgene Corporation 7 Powder Horn Drive Warren, New Jersey 07059		4. SUBMISSION TYPE: PA 5. DOCUMENT(S) NUMBER(S) DATE(S) SCF-020/AZ 8/7/02
6. NAME OF DRUG Thalomid	7. NONPROPRIETARY NAME thalidomide	
8. SUPPLEMENT(S) PROVIDES FOR: a new formulation and new strengths for Thalomid (thalidomide) Capsules.		9. AMENDMENTS AND OTHER *(Reports, etc.)* DATES NC 7/3/02 BC 12/5/02
10. PHARMACOLOGICAL CATEGORY Immunomodulator	11. HOW DISPENSED |X| Rx | | OTC	12. RELATED IND/NDA/DMF(S) N20-785/SLR-021
13. DOSAGE FORM(S) Capsule	14. POTENCY(IES) 50-, 100- and 200-mg	
15. CHEMICAL NAME/STRUCTURE (1) N-(2,6-dioxo-3-piperidyl)phthalimide (2) α-(N-phthalimido)glutarimide		16. MEMORANDA facsimile to Celgene: 7/26/02 telephone: 12/4/02, 12/5/02

17. COMMENTS

Supplement SCF-020, first submitted February 1, 2002, describes a reformulated drug product to be marketed in 50-, 100- and 200-mg strengths. Several deficiencies were noted in Chemistry Review #1 and in the Biopharmaceutics review by Dr. K. Kumi. An approvable letter (AE) was issued July 1, 2002. The current resubmission addresses all the issues noted, and includes dissolution data for current and proposed products under compendial conditions, and [redacted] The dissolution data support the request for a BE waiver for the new 100-mg capsule (see review by Dr. S. Jang, OCPB). The dissolution data, while limited, support dissolution testing at [redacted] Celgene has reluctantly agreed to use this method. An acceptance criteria of NLT [redacted] dissolved (Q) in [redacted] minutes has been agreed (see 12/5/02 amendment). Celgene has made a commitment to [redacted] if supported by additional data.

The section of SCF-020 covering labeling (package insert, blisters, cartons) was previously re-coded as SLR-021 since additional input from the clinical review team was required. Several changes to the proposed labeling have been recommended by DMETS and the clinical review team, and will be conveyed to Celgene in an approvable letter for SLR-021.

The dissolution data provided in the resubmission also indicate that all strengths of the reformulated product pass the current USP thalidomide capsule monograph dissolution test. Therefore, no special statements in the labeling are necessary at this time.

18. CONCLUSIONS AND RECOMMENDATIONS

From the chemist's perspective the outstanding issues related to the dissolution method and acceptance criteria identified in the initial chemistry review and by Dr. Kumi, and detailed in the July 1, 2002 approvable letter, have been adequately addressed. It is therefore recommended that this supplemental application be approved as soon as the issues related to labeling (SLR-021) are adequately addressed.

19. REVIEWER	SIGNATURE	DATE COMPLETED
Mark R. Seggel	{See appended electronic signature page}	December 5, 2002

20. CONCURRENCE: HFD-590/NSchmuff {See appended electronic signature page}

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Chemistry Review

Chem Review 2a

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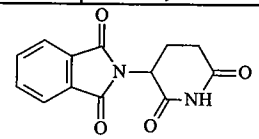
/s/

Mark Seggel
12/6/02 04:55:20 PM
CHEMIST
N20-785/S-020

Norman Schmuff
12/6/02 05:20:16 PM
CHEMIST

SUPPLEMENTAL NDA CHEMISTRY REVIEW #1	1. ORGANIZATION HFD-590	2. NDA NUMBER 20-785
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Celgene Corporation 7 Powder Horn Drive Warren, New Jersey 07059		4. SUBMISSION TYPE: PA 5. DOCUMENT(S) NUMBER(S) SLR-021 DATE(S) 5/24/02
6. NAME OF DRUG Thalomid	7. NONPROPRIETARY NAME thalidomide	
8. SUPPLEMENT(S) PROVIDES FOR: (a) labeling for Thalomid (thalidomide) 50 mg, 100 mg, and 200 mg Capsules, including package insert, blister pack cards, and cartons; (b) changes to the labeling to comply with Enhanced S.T.E.P.S.		9. AMENDMENTS AND OTHER *(Reports, etc.)* DATES BL 5/30/02 BL 8/26/02
10. PHARMACOLOGICAL CATEGORY Immunomodulator	11. HOW DISPENSED |X| Rx | | OTC	12. RELATED IND/NDA/DMF(S) N20-785/SCF-020
13. DOSAGE FORM(S) Capsule	14. POTENCY(IES) 50-, 100- and 200-mg	
15. CHEMICAL NAME/STRUCTURE (1) N-(2,6-dioxo-3-piperidyl)phthalimide (2) α-(N-phthalimido)glutarimide		16. MEMORANDA DMETS Consultation Response, 7/24/02

17. COMMENTS

Supplement SCF-020, first submitted February 1, 2002, describes a reformulated drug product to be marketed in 50-, 100- and 200-mg strengths. The three strengths are manufactured from a common halidomide blend. Product labeling (revised package insert and cartons reflecting new formulation and strengths) was submitted in amendments dated May 24, 2002 and May 30, 2002. These submissions were re-coded as a separate labeling supplement, SLR-021, for review by multiple disciplines, including ODS/DMETS.

Changes to the package insert include revised Description and How Supplied sections that accurately reflect the new product formulation and appearance of each strength. The new blister cards and cartons include all appropriate information. However, DMETS has raised several valid concerns regarding the format and appearance of the blister cards and cartons. Several recommendations will be conveyed to Celgene in the approvable letter.

A number of other minor editorial changes to the package insert and changes to comply with the Enhanced S.T.E.P.S. are under review by the clinical review team.

18. CONCLUSIONS AND RECOMMENDATIONS

The Description and How Supplied sections of the package insert are acceptable. The information on the blister cards and cartons is also acceptable, however DMETS has several recommendations regarding format and appearance. It is recommended that an approvable letter be issued for this supplement, pending submission of labeling satisfying the concerns of the clinical review team and DMETS.

19. REVIEWER	SIGNATURE	DATE COMPLETED
Mark R. Seggel	{See appended electronic signature page}	December 5, 2002

20. CONCURRENCE: HFD-590/NSchmuff {See appended electronic signature page}

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/s/

Mark Seggel
12/6/02 05:01:47 PM
CHEMIST
N20-785/S-021

Norman Schmuff
12/6/02 05:25:30 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-785 / S-020, S-021

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	20-785 SCS-020
Generic Name:	Thalidomide
Brand Name:	Thalomid®
Dosage Strengths:	50, 100, 200 mg
Dosage Form:	Oral capsules
Indication:	Thalidomide is indicated for the acute treatment of the cutaneous manifestation of moderate to severe erythema nodosum leprosum (ENL). Thalidomide is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestation of ENL recurrence
Dosage and Administration:	For an episode of cutaneous ENL, thalidomide should be initiated at 100 to 300 mg/day, administered once daily with water, preferably at bedtime and 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, thalidomide dosing may be initiated at higher doses up to 400 mg/day once daily or in divided doses with water, at least 1 hour after meals.
Applicant:	Celgene Corporation
OND Clinical Division:	DSPIDP (HFD-590)
OCPB Division:	DPEIII (HFD-870)
Submission Type:	Chemistry Supplement
Submission Dates:	3/1/02, 4/5/02
Review Date:	6/28/02
Reviewer:	Kofi A. Kumi, Ph.D.
Team Leader:	Barbara Davit, Ph.D.

Executive Summary

This Chemistry, Manufacturing and Controls (CMC) supplement contains information pertaining new formulations and new strengths for Thalomid® (thalidomide) capsules. The sponsor plans to replace the current approved commercial 50 mg capsules with a new 50 mg capsule formulation. In addition, a 100 mg and 200 mg strength capsule has been developed which the sponsor proposes to introduce for marketing. A bioequivalence (BE) study report comparing the marketed 50 mg Thalomid capsule to the lowest and highest strengths (50 and 200 mg capsules) of these newly formulated Thalomid capsules is included in the application. The amendment contains information on the development of a new dissolution methodology for thalidomide 50mg, 100mg and 200 mg strengths. There is a current USP monograph for thalidomide dissolution methodology. The sponsor contends that this compendium methodology was developed and validated for use with the current thalidomide 50 mg formulation and is inappropriate for the 100

mg and 200 mg proposed strengths. The sponsor also request a waiver of bioequivalence study comparing the 100 mg capsule to the approved 50 mg capsule. The new 50, 100 and 200 mg thalidomide formulations are proportional in composition.

The study demonstrated that the 50 mg reformulated capsule is bioequivalent to the approved commercial 50-mg capsule. The 200-mg capsule is bioequivalent to the reformulated 50 mg capsule but did not pass BE criteria when compared to the approved commercial 50 mg capsule. The 90% CI for Cmax was not contained within the regulatory BE criteria of 80% to 125%; the 90% CI was 79.5% to 92.2%. The 90% CI for AUC(0-t) and AUC(0-∞) were contained within the acceptable range for BE. The current 50 mg reference capsule is to be replaced by the reformulated 50 mg capsule.

The following dissolution method and specification were proposed by the sponsor to replace the current USP approved method and specification:

USP Apparatus:
Paddle Speed:
Medium:
Volume:
Vessel temperature:

Specification:

Comments (#3 to #5 should be sent to the sponsor)

1) This reviewer concurs with the sponsor's conclusion that since the reformulated 50 mg capsule will replace the approved commercial 50 mg capsule, the fact that the 90% CI for Cmax failed to meet the regulatory criteria for the 200 mg strength versus the currently approved 50 mg capsule should not be of clinical significance.

2) There is insufficient dissolution data and profiles provided for the 50 mg, 100 mg and 200 mg thalidomide capsules to adequately validate the proposed method and specification. Insufficient dissolution profiles using the proposed media for the 100 mg capsules compared to the currently approved 50 mg capsule were supplied. This did not allow satisfactory evaluation of the dissolution profile for the 100 mg capsule.

3) The sponsor should conduct dissolution testing using rpm at the three new strengths of thalidomide and compare them to the approved 50 mg capsule. The test should be conducted on 12 units of thalidomide capsules for each thalidomide dosage strength.

4) The sponsor should provide individual and mean dissolution data and profiles comparing the 50, 100 and 200 mg capsules to the approved 50 mg capsule using the proposed method at 75 and 100 rpm and also using

5) Individual and mean dissolution data and profiles comparing the 100 mg to the approved 50 mg capsule using an appropriate and acceptable media should be provided to facilitate consideration of the waiver of a bioequivalence study comparing the two strengths. The dissolution test should be conducted with 12 units of each approved 50 mg capsule and the proposed 100 mg capsule. The sponsor should compute the similarity factor (f2) comparing the dissolution profiles requested.

Recommendation

Based on the human Pharmacokinetic and Bioavailability data submitted in this CMC supplement, the new 50 mg and 200 mg strengths of thalidomide capsules are acceptable. However, it is recommended that the sponsor provide adequate and sufficient dissolution data and profiles for the reformulated 50, 100 and 200 mg strengths of thalidomide addressed in the comments above and in the chemistry review before full approval is granted. It is recommended that the waiver of BE study comparing the 100 mg to the approved 50 mg thalidomide capsules not be granted until the dissolution information requested is provided and found acceptable upon review.

Kofi A. Kumi, Ph.D.
Reviewer,
Clin. Pharmacology and Biopharm
HFD-590 Section
DPEIII/OCPB

Concurrence

Barbara Davit, Ph.D.
Team Leader
Clin. Pharmacology and Biopharm.
HFD- 590 Section
DPEIII/OCPB

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Summary of Clinical Pharmacology and Biopharmaceutics Findings

The sponsor conducted a bioequivalence study to assess the bioequivalence of 2 new capsule formulations of thalidomide (50 mg and 200 mg) compared with the marketed 50 mg capsule formulation of thalidomide (Thalomid®) following a single 200 mg dose, administered in the fasted state. The following tables provide the statistical comparisons of the formulations tested in this study.

Tale 1: Treatment A versus Treatment C

Parameter	Treatment A	Treatment C	Mean Ratio	90% CI
Ln (Cmax)	7.411	7.530	88.8	82.5 – 95.5
Ln (AUC(0-t))	9.846	9.928	92.1	89.2 – 95.1
Ln (AUC(0-∞))	9.993	10.016	97.8	93.8 – 101.9

Treatment A = 4 x 50 mg Thalidomide capsules: test formulation
Treatment C = 4 x 50 mg Thalomid (Thalidomide) capsule: reference
Values for Treatments A and C are the least square means (LSMEANS) from ANOVA
Mean Ratio = 100 * exp(test – reference) for Ln-transformed parameters

Table 2: Treatment B versus Treatment C

Parameter	Treatment B	Treatment C	Mean Ratio	90% CI
Ln (Cmax)	7.375	7.530	85.6	79.5 – 92.2
Ln (AUC(0-t))	9.834	9.928	91.0	88.1 – 93.9
Ln (AUC(0-∞))	10.003	10.016	98.7	94.7 – 103.0

Treatment B = 1 x 200 mg Thalidomide capsules, New Formulation: test formulation
Treatment C = 4 x 50 mg Thalomid (Thalidomide) capsule: reference
Values for Treatments A and C are the least square means (LSMEANS) from ANOVA
Mean Ratio = 100 * exp. (test – reference) for Ln-transformed parameters

Tale 3: Treatment A versus Treatment B

Parameter	Treatment A	Treatment B	Mean Ratio	90% CI
Ln (Cmax)	7.411	7.35	103.7	96.3 – 111.6
Ln (AUC(0-t))	9.846	9.834	101.3	98.1 – 104.6
Ln (AUC(0-∞))	9.993	10.003	99.0	94.9 – 103.2

Treatment A = 4 x 50 mg Thalidomide capsules: test formulation
Treatment B = 1 x 200 mg Thalidomide capsule: test formulation
Values for Treatments A and B are the least square means (LSMEANS) from ANOVA
Mean Ratio = 100 * exp. (test – reference) for Ln-transformed parameters.

The 90% confidence intervals (CI) indicate that the 50 mg new formulation is bioequivalent to the marketed formulation. Similarly, comparison of the new 50 mg formulation to the new 200 mg formulation indicated that the two formulations were bioequivalent. However, a comparison of the new 200 mg formulation to the approved, commercial 50 mg indicated that the 90% CI for Cmax was 79.5 % - 92.2% which is not contained within the regulatory criteria of 80 to 125%. The 90% CI for AUC(0-t) and AUC(0-∞) were within the acceptable range for bioequivalence. The current 50 mg reference capsule is to be replaced by the reformulated 50 mg capsule, which is bioequivalent to the 200 mg capsule.

This reviewer agrees with the sponsor's conclusion that since the reformulated 50 mg capsule will replace the approved commercial 50 mg capsule, the fact that the 90% CI for Cmax failed to meet

the regulatory criteria for the new 200 mg capsule versus the presently approved 50 mg capsule should not be of clinical significance; AUC passed indicating the extent of absorption was equivalent after administration of equal doses of the reformulated 50 and 200 mg capsules when compared to the commercial 50 mg capsules. Therefore, the reformulated 50 and 200 mg thalidomide capsules are acceptable dosage strengths of thalidomide and the reviewer recommends approval.

Dissolution: Thalidomide (Thalomid) is currently marketed as a 50 mg capsule. The sponsor is currently developing higher strength dosage forms and as a result has developed a reformulated blend that will fill into three dosage strengths, 50, 100 and 200 mg capsules.

There is USP compendium methodology for dissolution. The current compendium method for the currently approved 50 mg capsules of Thalomid is the following:

Apparatus:
Paddle Speed:
Medium:

Volume:
Vessel temperature:

Specification:

The sponsor states that the current compendium dissolution methodology was developed and validated for use with the current formulation (Thalomid™ 50 mg capsules). Thalidomide has a solubility approximately in the current medium. The solubility is constant between sponsor states that the compendia method will be amenable for use in testing the reformulated thalidomide 50 mg capsule but will not be suitable the 100 and 200 mg capsules since sink conditions will not be met at the specified volume of Therefore rather than separate methods for each of the strengths, a single method was developed to test the reformulated material regardless of strength. The sponsor is proposing the following dissolution method for thalidomide 50, 100 and 200 mg capsules:

Apparatus:
Paddle Speed:
Medium:
Volume:
Vessel temperature:

Specification:

The sponsor did not provide sufficient dissolution profiles for the three thalidomide strengths, especially the 100 and 200 mg strengths to allow the determination of the appropriateness of the proposed dissolution method and specification. The sponsor did not provide adequate information to compare the dissolution profile using a paddle speed with the proposed method to allow determination of the appropriate paddle speed for the proposed method. Insufficient dissolution profiles using the proposed media for the 100 mg capsules compared to the currently approved 50 mg capsule were supplied to allow adequate evaluation of the 100 mg capsule.

The sponsor should provide individual and mean dissolution data and profiles comparing the currently marketed 50 mg, the new 50, 100 and 200 mg capsules using the proposed method at a paddle spe[illegible] and also using [illegible] The dissolution test should be conducted on 12 units for each strength of thalidomide capsule.

The sponsor had requested a biowaiver for the 100 mg thalidomide capsules. The quantitative composition and components of the 100 mg capsules is proportional to the new 50 mg and 200 mg capsules which are bioequivalent. The sponsor did not provide sufficient dissolution data and profile using the USP methodology comparing the 100 mg capsule to the approved 50 mg capsules and the proposed dissolution method is not acceptable. Hence, this reviewer recommends that the biowaiver should not be granted until the dissolution issues are resolved and an acceptable data and profile using an acceptable methodology are provided.

Question Based Review

Is the reformulated thalidomide 50 mg and 200 mg capsules bioequivalent to the approved 50 mg capsule?

The sponsor conducted a bioequivalence (BE) study to demonstrate that 2 new formulations of thalidomide (50 mg and 200 mg) are bioequivalent to the currently approved 50 mg capsule. The study demonstrated that the 50 mg reformulated capsule is bioequivalent to the approved commercial 50-mg capsule. The 200-mg capsule is bioequivalent to the reformulated 50 mg capsule but not to the approved commercial 50 mg capsule. 90% CI for Cmax was not contained within the BE criteria; the lower bound CI was 79.5% instead of the required 80%. The 90% CI for AUC(0-t) and AUC(0-∞) were contained within the regulatory acceptable range for bioequivalence. The current 50 mg reference capsule is to be replaced by the bioequivalent, reformulated 50 mg capsule. This reviewer agrees with the sponsor's conclusion that since the reformulated 50 mg capsule will replace the approved commercial 50 mg capsule, the fact that the 90% CI for Cmax for the 200 mg capsule versus the present 50 mg capsule failed to meet the regulatory criteria should not be of clinical significance.

Title (Protocol 466-02): A 200 mg Single Dose, Bioequivalence Study of Three Thalidomide Formulations: 50 mg Marketed Capsule, 50 mg New Capsule and 200 mg New Capsule in Healthy, Male and/or Female Volunteers

Objective: To assess the bioequivalence of 2 new capsule formulations of thalidomide (50 mg and 200 mg) compared with the marketed 50 mg capsule formulation of thalidomide (Thalomid®) following a single 200 mg dose, administered in the fasted state

Study Design: This study was a single dose, randomized, open-label, 3-way crossover design. Thirty subjects were enrolled but 23 subjects completed the study. The mean age and weight were 38 ± 13 years and 173.3 ± 26.8 lbs., respectively. The subjects were randomized into 6 dosing sequence groups with 5 subjects per group. Each dose was a single 200 mg dose of thalidomide (either the test or reference product taken) after an overnight fast. The following treatments were administered to the subjects:

Treatment A: Thalidomide 4 x 50 mg capsule (new formulation) (Lot 0202T)
Treatment B: Thalidomide 200 mg capsule (new formulation) (Lot 0196T)
Treatment C: Thalomid (Thalidomide) 4 x 50 mg current, commercial capsule (Lot 0403S)

Blood samples (7 mL) were collected during each study period at hour 0 (predose), and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16 and 24 hours predose. An LC/MS/MS method was developed and validated for the determination of thalidomide in human heparinized plasma. The validated method had a linear range of om a heparinized plasma sample. The LOQ wa

Tale 4: The quantitative composition of the new thalidomide formulations is provided in the following table.

Component	Quantity (mg/200 mg capsule)	Quantity (mg/100 mg capsule)	Quantity (mg/50 mg capsule)
Thalidomide	200	100	50
Pre-gelatinized Corr Starch, NF			
Magnesium Stearate NF			
Size of Hard Gelatii Capsule			

Table 5: The quantitative composition for the currently approved 50 mg formulation is provided in the following table.

Component	Quantity (mg/50 mg capsule)
Thalidomide	50

Results: Similar thalidomide concentration profiles were obtained when the three treatments are compared. Both test formulations resulted in lower mean peak plasma thalidomide concentrations compared to the reference formulation. A summary of the pharmacokinetic parameters are provided in the following table

Table 6

Pharmacokinetic Parameter	Treatment A	Treatment B	Treatment C
	Mean ± SD		
Cmax (ng/mL)	1685.5 ± 299.24	1644.5 ± 369.29	1922.7 ± 402. 08
Tmax (hr)	4.15 ± 1.81	4.03 ± 1.54	3.87 ± 1.97
AUC(0-t)(ng*hr/mL)	19327 ± 3092.6	19136 ± 3060.5	21032 ± 3151
AUC(0-∞)(ng*hr/mL)	22611 ± 4039.9	22914 ± 23118	23118 ± 4045.7
T ½ (hr)	7.90 ± 2.22	8.59 ± 3.44	6.14 ± 1.77
Kel 1/hr)	0.0939 ± 0.0243	0.09214 ± 0.0291	0.121 ± 0.0294
MRT (hr)	13.04 ± 2.685	13.83 ± 4.580	10.82 ± 2. 385

Treatment A = 4 x 50 mg Thalidomide Capsules, New Formulation: test
Treatment B = 1 x 200 mg Thalidomide Capsule, New Formulation: test
Treatment C = 4 x 50 mg Thalomid (Thalidomide) Capsules, Marketed Formulation: reference

The following tables provide the statistical comparisons on Ln-transformed Cmax, AUC(0-t) and AUC(0-∞).

Tale 7: Treatment A versus Treatment C

Parameter	Treatment A	Treatment C	Mean Ratio	90% CI
Ln (Cmax)	7.411	7.530	88.8	82.5 – 95.5
Ln (AUC(0-t))	9.846	9.928	92.1	89.2 – 95.1
Ln (AUC(0-∞))	9.993	10.016	97.8	93.8 – 101.9

Treatment A = 4 x 50 mg Thalidomide capsules: test formulation
Treatment C = 4 x 50 mg Thalomid (Thalidomide) capsule: reference
Values for Treatments A and C are the least square means (LSMEANS) from ANOVA
Mean Ratio = 100 * exp(test – reference) for Ln-transformed parameters

Table 8: Treatment B versus Treatment C

Parameter	Treatment B	Treatment C	Mean Ratio	90% CI
Ln (Cmax)	7.375	7.530	85.6	79.5 – 92.2
Ln (AUC(0-t))	9.834	9.928	91.0	88.1 – 93.9
Ln (AUC(0-∞))	10.003	10.016	98.7	94.7 – 103.0

Treatment B = 1 x 200 mg Thalidomide capsules, New Formulation: test formulation
Treatment C = 4 x 50 mg Thalomid (Thalidomide) capsule: reference
Values for Treatments A and C are the least square means (LSMEANS) from ANOVA
Mean Ratio = 100 * exp(test – reference) for Ln-transformed parameters

Table 9: Treatment A versus Treatment B

Parameter	Treatment A	Treatment B	Mean Ratio	90% CI
Ln (Cmax)	7.411	7.35	103.7	96.3 – 111.6
Ln (AUC(0-t))	9.846	9.834	101.3	98.1 – 104.6
Ln (AUC(0-∞))	9.993	10.003	99.0	94.9 – 103.2

Treatment A = 4 x 50 mg Thalidomide capsules: test formulation
Treatment B = 1 x 200 mg Thalidomide capsule: test formulation
Values for Treatments A and B are the least square means (LSMEANS) from ANOVA
Mean Ratio = 100 * exp. (test – reference) for Ln-transformed parameters.

The study assessed the bioequivalence (BE) of 2 new capsule formulations of thalidomide (50 and 200 mg) compared with the marketed 50 mg capsule formulations of thalidomide (Thalomid®) following a single 200 mg dose administered in the fasted state.

The 90% confidence intervals (CI) indicate that the 50 mg new formulation is bioequivalent to the marketed formulation. Similarly, comparison of the new 50 mg formulation to the new 200 mg formulation indicated that the two formulations were bioequivalent. However, a comparison of the new 200 mg formulation to the approved, commercial 50 mg indicated that the 90% CI for Cmax was 79.5 % - 92.2% which is not contained within the regulatory criteria of 80% to 125%. The 90% CI for AUC(0-t) and AUC(0-∞) were within the acceptable range for bioequivalence. The current 50 mg reference capsule is to be replaced by the bioequivalent, reformulated 50 mg capsule, to which the 200 mg capsule met bioequivalence requirements.

Reviewer Comments: This reviewer agrees with the sponsor's conclusion that since the reformulated 50 mg capsule will replace the approved commercial 50 mg capsule, the fact that the 90% CI for Cmax failed to meet the regulatory criteria should not be of clinical significance; AUC passed indicating the extent of absorption was equivalent after administration of equal

doses of the reformulated 50 and 200 mg capsules when compared to the commercial 50 mg capsules. Therefore, the reformulated 50 and 200 mg thalidomide capsules are acceptable dosage strengths of thalidomide and the reviewer recommends approval.

Are there adequate dissolution data and profile to validate the proposed dissolution method and specification for thalidomide 50 mg, 100 mg and 200 mg capsules?

There is insufficient dissolution profiles provided for the 50 mg, 100 mg and 200 mg thalidomide capsules to adequately validate the proposed method and specifications. The sponsor should conduct additional dissolution testing using the three new strengths of thalidomide and compared to the approved 50 mg capsule. The test should be conducted on 12 units of thalidomide capsules.

Thalolidomide (Thalomid®) is currently marketed as a 50 mg capsule. The sponsor is currently developing higher strength dosage forms and as a result has developed a reformulated blend that will fill into three dosage strengths, 50, 100 and 200 mg capsules. The sponsor intends to replace the currently marketed 50 mg capsules with the reformulated 50 mg capsule. The proportions used for the reformulated blend are listed in the table below

Table 10

Component		
Thalidomide		
Pregelatinized Corn Starch		
Magnesium Stearate		

The sponsor states that, the current compendium dissolution methodology was developed and validated for use with the current formulation (Thalomid® 50 mg capsules). Thalidomide has a solubility limit of approximatel the current medium. The solubility is constant between . The compendium method will be amenable for use in testing the reformulated thalidomide 50 mg capsule but will not be suitable for the 100 and 200 mg capsules since sink conditions will not be met at the specified volume Therefore rather than separate methods for each of the strengths, a single method was developed to test the reformulated material regardless of strength.

The current compendia method for old 50 mg capsules of Thalomid®

Apparatus:
Paddle speed:
Media:

Vessel temperature:

Specification:

A dissolution method was tested that contained various surfactants was selected and the solubility of thalidomide was tested at different centrations. Thalidomide solubility in µg/mL, respectivelv. ution with higher concentration resulted in a solution pH of more tha ue to the spontaneous hydrolysis of thalidomide in solutions with pH values abov the SLS solution was adjusted to a lower with dissolution medium.

The sponsor reported that the choice o [redacted] oncentration was based on the ability to meet sink conditions and be amenable to routine easy usage. [redacted] at p [redacted] re determined to be the likely conditions to produce sink conditions for both the lower, 50 mg and higher, 200 mg capsules. A comparative dissolution test indicate similar profiles of % dissolved thalidomide are obtained for the 50 mg strength capsules in [redacted] pH [redacted] edia but different profiles were obtained for the 200 mg strength capsule. The dissolution test was conducted on 2 capsules for each SLS concentration and thalidomide strength. The % of thalidomide 200 mg dissolved at the 60 min time point [redacted] The sponsor indicated that this implied the solubilization kinetics played a limited role and the 200 mg strength dissolution is more release dependent i[redacted] media. Hence, [redacted] is proposed as the dissolution medium.

The agitation speed of the paddle in the proposed method was examined a[redacted] RPM. The sponsor selected [redacted] for the new method because the % dissolved of thalidomide was lower with the proposed method a[redacted] compared to that with compendium method. The [redacted] was tested using 2 capsules at 50 mg and 2 capsules at the 200 mg strength. Equivalence between the current compendium dissolution method and the new proposed method was evaluated by performing a dissolution test on 12 and 6 capsules, respectively, of the reformulated 50 mg capsules. The f2 calculated for comparison of the dissolution method was 44.09 with the old method as reference. The sponsor stated that this indicated the two methods are not similar. The sponsor indicates this difference is due to capsule shell solubilization dynamics at the 15 mins time point. If this time point is eliminated, the calculated f2 = 52.1 and the two dissolution methods are similar.

The following is the proposed method and specification

Proposed Dissolution Method

USP Apparatus:
Medium:
Volume:
Paddle Speed:
Vessel temperature:

Specification:

Reviewer Comments on Dissolution Methodology Development :

Upon discussions with the chemistry reviewer, it was learned that the compendium dissolution method developed by FDA lab in St. Louis was intended for 100 mg thalidomide as well. Please refer to the CMC reviewer's review.

The chemistry reviewer indicated the dissolution test for the stability batches was conducted usin[redacted] but the sponsor is proposing a media wi[redacted]

The sponsor is using f2 calculations to validate methods. This is not acceptable since f2 is not intended to be used to compare and validate dissolution methods.

The sponsor did not provide adequate information to compare the dissolution profile using a paddle speed of [redacted] with the proposed method to allow determination of the appropriate paddle speed for the proposed method.

The sponsor should provide individual and mean dissolution data and profiles compari[redacted]the 50, 100 and 200 mg tablets using the proposed method and also using [redacted] at 75 an[redacted] rpm.

Has adequate dissolution data been provided to grant a biowaiver of the 100 mg thalidomide capsules?

Insufficient dissolution profiles using the proposed media for the 100 mg capsules compared to the currently approved 50 mg capsule were supplied to allow adequate evaluation of the 100 mg capsule. Additional dissolution profiles comparing the 100 mg to the approved 50 mg capsule using the proposed media should be provided to facilitate consideration of the waiver of a bioequivalence study comparing the two strengths.

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/s/

Kofi Kumi
6/28/02 04:44:23 PM
BIOPHARMACEUTICS

Barbara Davit
6/28/02 06:19:04 PM
BIOPHARMACEUTICS

Clinical Pharmacology and Biopharmaceutics Response

NDA: 20-785 SCS020
Drug: Thalidomide (Thalomid)
Sponsor: Celgene
Submission Date: 7/3/02
Review Date: 7/24/02

Reviewer: Kofi A. Kumi, Ph.D.
Team Leader: Barbara Davit, Ph.D.

Background: Celgene was issued approvable letter for NDA 20-785 SCS020. Celgene wanted clarification of the items discussed in the approvable letter.

Clarification on Items 1 and 2:

a) The dissolution testing should be conducted on a single unit of each dosage strength per vessel. That is, for example, in comparing the approved 50 mg capsule to the proposed 200 mg capsule, one unit of the 50 mg capsule should be compared to one unit of the 200 mg capsule in each of the 12 determinations for each condition requested.

b) It is recommended that f2 be calculated for all dissolution profile comparisons using the same media and method.

Clarification to question 3

a) Testing at an additional pH is not necessary for dissolution waiver of an immediate release product. However, if you wish to test at an additional pH [redacted] ceptable.

b) Similar to clarification for items 1 and 2 above, the dissolution profile for one unit of 50 mg capsule should be compared with one unit of the 100 mg capsule. In addition, you should provide dissolution profile comparisons of the proposed 100 mg capsule to the proposed 50 and 200 mg capsules using the compendia media and method. The test should be conducted on 12 units of each dosage strength and f2 should be calculated for each dissolution comparison using the same media and method.

Kofi A. Kumi, Ph.D.
Reviewer
Clin.Pharm./Biopharm.
HFD-590 Section
DPE3/OCPB

Concurrence

Barbara Davit, Ph.D.
Team Leader
Clin.Pharm./Biopharm.
HFD-590 Section
DPE3/OCPB

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/s/

Kofi Kumi
8/15/02 03:08:48 PM
BIOPHARMACEUTICS

Hard copy signed as on 8/6/02

Barbara Davit
8/15/02 03:49:29 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-785	Submission Date(s): August 7, 2002
Brand Name	THALOMID™
Generic Name	Thalidomide
Reviewer	Seong H. Jang, Ph.D.
Team Leader	Barbara Davit, Ph.D.
OCPB Division	DPEIII
OND Division	DSPIDP
Applicant	Celgene Corporation
Relevant IND(s)	
Submission Type; Code	Resubmission; BC
Formulation; Strength(s)	50, 100, 200 mg capsules
Indication	The acute treatment and maintenance treatment of the cutaneous manifestation of erythema nodosum leprosum (ENL)

I. BACKGROUND

On March 1, 2002, the applicant submitted an NDA for its product, 50, 100 and 200 mg thalidomide capsules. The application was approvable. The approvable letter was sent on July 1, 2002. The applicant planned to (a) replace the current approved commercial 50 mg capsule with a new 50 mg capsule formulation and (b) develop two additional strength capsules, i.e., 100 and 200 mg. A bioequivalence (BE) study showed that the marketed 50 mg thalidomide capsule is bioequivalent to the newly formulated 50 and 200 mg capsules. The applicant requested a waiver of in vivo BE testing for 100 mg capsule, based on dissolution data. In addition, the sponsor wanted to use a new dissolution method rather than the previously approved USP method. A detailed description of the new and old formulations, in vivo BE study and dissolution study can be found in the Clinical Pharmacology and Biopharmaceutics (CPB) Review by Dr. Kofi Kumi, dated 6/28/02. In the approvable letter, the applicant was asked to provide additional dissolution data from different dissolution conditions, including different concentrations of and different paddle speed. In this submission, the sponsor responded to the FDA issues presented in the approvable letter of 7/06/02.

II. Dissolution method

A detailed description of the dissolution method was provided in the previous CPB Review, dated 6/28/02. Briefly, the proposed method is as follows;

Apparatus:
Dissolution medium:
Volume:
Paddle speed:
Temperature:

Specification:

To verify this dissolution method, the sponsor was asked to provide additional dissolution data at different concentration of SLS, i.e., and different paddle speed, i.e., 75 and 100 rpm. In addition, dissolution data from the USP method were also requested. The present approved USP method is as follows;

Apparatus:
Dissolution medium:
Volume:
Paddle speed:
Temperature:

Specification:

Dissolution data at each condition are summarized in Tables 1 to 5.

Table 1. Percent dissolution of approved 50 mg capsule and new formulation capsules in
100 rpm.

	Average % dissolved (%RSD)

Table 2. Percent dissolution of approved 50 mg capsule and new formulation capsules in SLS at 100 rpm.

	Average % dissolved (%RSD)

Table 3. Percent dissolution of approved 50 mg capsule and new formulation capsules in at 75 rpm.

	Average % dissolved (%RSD)

Table 4. Percent dissolution of approved 50 mg capsule and new formulation capsules in SLS at 75 rpm.

	Average % dissolved (%RSD)

Table 5. Percent dissolution of approved 50 mg capsule and new formulation capsules in [redacted] compendial medium.

[redacted]

The sponsor proposed [redacted] as a new dissolution method based on f_2 values calculated using all the data points. However, f_2 should be calculated using time points before and only one point after both tablet formulations achieve 85% dissolution. Individual dissolution data are attached in Appendix.

Reviewer's comment: *As shown in Tables 3 and 4, at [redacted], dissolution did not meet the current NDA and USP acceptance criteria, i[redacted]issolved in 60 min, for all three strength (Tables 3 and 4). Therefore, the two conditions did not seem appropriate. On the other hand, at [redacted] dissolution met the current NDA and USP acceptance criteria for all three strength (Tables 1 and 2), indicating that both methods may be appropriate for routine QC dissolution testing. However, the comparison of dissolution data at two conditions, i.e., [redacted] showed that dissolution i[redacted] much faster and, hence, less discriminating than [redacted] For example, [redacted] rpm, the f_2 metric cannot be calculated for any strength because only one data point, i.e., at 15 min, is less than 85%. The comparison of two conditions with the approved USP method also showed that [redacted] -100 rpm is closer to the USP method than [redacted] igures 1 to 3 showed the comparison of dissolution profiles of each strength at different conditions. Based on the comparison of dissolution rate and discriminating power, CPB reviewer concluded that [redacted] s appropriate as a new dissolution method.*

Figure 1. Comparison of dissolution rate of newly formulated 50 mg capsule in 4 L compendial medium and [redacted]

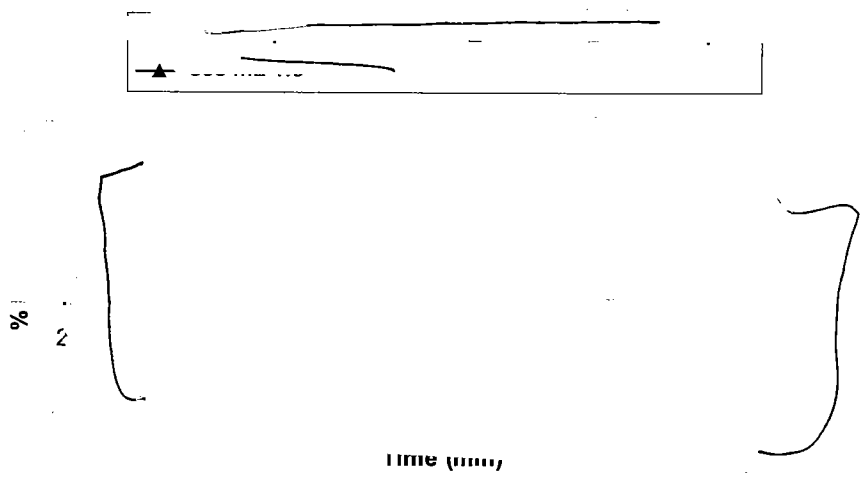


Figure 2. Comparison of dissolution rate of newly formulated 100 mg capsule in 4 L compendial medium and

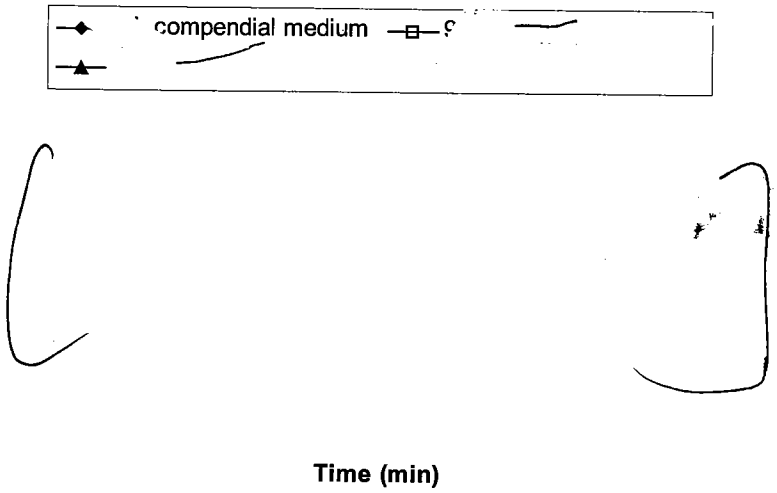
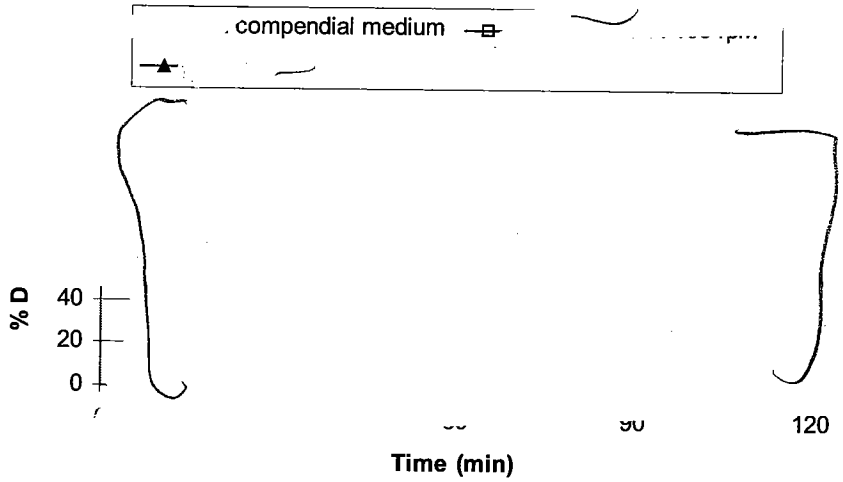


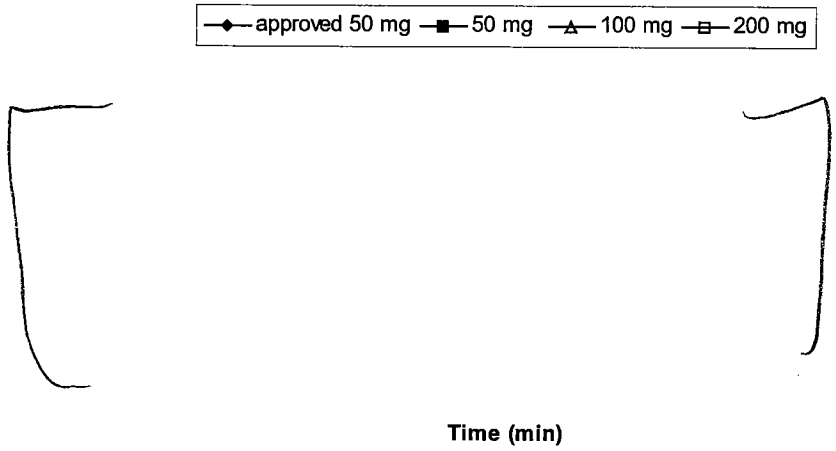
Figure 3. Comparison of dissolution rate of newly formulated 200 mg capsule i mpendial medium and



III. BE waiver for 100 mg capsule

In the original submission, results of the in vivo BE study showed that the marketed 50 mg and newly formulated 50 and 200 mg capsules are bioequivalent. Dissolution data in the approved USP method are appropriate to approve BE waiver of the 100 mg capsule; f_2 value obtained from the dissolution profiles of 100 and 200 mg capsule, 73, recalculated by reviewer, were higher than 50. The results are summarized in Table 5 and figure 4.

Figure 4. Dissolution of approved 50 mg capsule and new formulation capsules in th pendial medium.



IV. RECOMMENDATION

1. The following dissolution method using f medium volume is recommended, with the interim specification shown below.

   Apparatus:
   Dissolution medium:
   Volume:
   Paddle speed:
   Temperature:

   Specification:

2. A waiver of in vivo bioequivalence testing for the 100 mg capsule is granted based on (1) proportional similarity with the bioequivalent 50 and 200 mg strengths, and (2) acceptable dissolution data obtained from the approved USP method.

Seong H. Jang, Ph.D.
Reviewer
Clinical Pharmacology and Biopharmaceutics
HFD-590
DPEIII/OCPB

Concurrence

Barbara Davit, Ph.D.
Team Leader
Clinical Pharmacology and Biopharmaceutics
HFD-590
DPEIII/OCPB

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/s/

Seong Jang
12/5/02 12:58:49 PM
BIOPHARMACEUTICS

Barbara Davit
12/5/02 03:44:16 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-785 / S-020, S-021

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Sammie Beam, Senior Regulatory Manager (CDER/OND/ODS/OPSS/DMETS/HFD-420)

FROM: Matthew A. Bacho, Regulatory Project Manager (Division of Special Pathogen and Immunologic Drug Products, HFD-590)

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 1, 2002		20-785/SLR-021	Labeling Supplement	May 24, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Thalomid®			August 1, 2002

NAME OF FIRM: Celgene Corporation

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- x OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: We request a review of the new package insert and carton labeling for Thalomid® 50, 100, and 200-mg capsules. Previously, Thalomid® was only available as a 50-mg capsule and the submission now under review involves a new formulation (the old 50-mg capsule will no longer be produced). Please evaluate the attached materials to assess whether they are designed to minimize/prevent erroneous dispensing. Note: The chemistry supplement linked to this submission, SCF-020, was given an "Approvable" action on July 1, 2002, and we expect the applicant to attend to the deficiencies over the next few weeks. Once this supplement is approved, Celgene will require an action on SLR-021 before they can market these capsules, and this is why the review needs to be completed in the timeframe noted above.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Matthew Bacho
7/1/02 03:38:12 PM
NDA 20-785/SLR-021

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
(DMETS; HFD-420)

DATE RECEIVED: 07/01/02	**DUE DATE:** 08/01/02	**ODS CONSULT #:** 02-0145

TO: Renata Albrect, M.D.
Acting Director, Division of Special Pathogen and Immunologic Drug Products
HFD-590

THROUGH: Matthew A. Bacho
Project Manager
HFD-590

PRODUCT NAME:	**MANUFACTURER:**
Thalomid (Thalidomide Capsules) 50 mg, 100 mg, and 200 mg **NDA #: 20-785/SLR-021**	Celgene Corporation

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Special Pathogen and Immunologic Drug Products (HFD-590), DMETS reviewed the proposed blister pack labels, carton and package insert labeling of Thalomid for possible interventions that may help minimize medication errors.

DMETS RECOMMENDATION: DMETS recommends the implementation of the proposed labeling in conjunction with the labeling revisions outlined in the review in order to minimize the potential for medication errors.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Rm. 15B32
Center for Drug Evaluation and Research

Label Review

DATE OF REVIEW: July 11, 2002

NDA: 20-785/SLR-021

NAME OF DRUG: **Thalomid**
(Thalidomide Capsules)
50 mg, 100 mg, and 200 mg

NDA HOLDER: Celgene Corporation

I. INTRODUCTION

This consult is in response to a July 1, 2002 request by the Division of Special Pathogen and Immunologic Drug Products to review the blister pack labels, carton and package insert labeling for possible interventions in minimizing medication errors.

Thalomid 50 mg capsules were approved by the Agency on July 16, 1998. However, on May 24, 2002, the sponsor, Celgene, submitted SLR-021, which proposes to reformulate the 50 mg capsules. The current Thalomid 50 mg capsules contain the following inactive ingredients: anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin. However, the reformulated Thalomid capsules will contain the following inactive ingredients: pregelatinized starch, magnesium stearate, titanium dioxide, and gelatin. Additionally, the sponsor proposes to market 100 mg and 200 mg capsules.

PRODUCT INFORMATION

Thalomid contains the active ingredient, thalidomide, which is an immunomodulatory agent. Thalomid is indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL). Thalomid is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence. For an episode of cutaneous ENL, Thalomid should be initiated at 100 mg to 300 mg/day, administered once daily. In patients with a severe cutaneous ENL reaction, Thalomid may be initiated at higher doses up to 400 mg once daily. Due to the risk of severe, life-threatening human birth defects, Thalomid may only be prescribed by prescribers registered with the System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.* ™) program. Additionally, Thalomid may only be dispensed by pharmacists registered with the *S.T.E.P.S.* ™ program. Thalomid will be available as 50 mg, 100 mg, and 200 mg capsules.

II. RISK ASSESSMENT

A. AERS SEARCH

DMETS searched the FDA Adverse Event Reporting System (AERS) database in order to determine any post-marketing safety reports of medication errors associated with *Thalomid.* The Meddra Preferred Term (PT), "Medication Error", and the drug names, "Thalomid%" and "Thalidomide%" were used to perform the search. This search strategy revealed three reports, one concerning name confusion and two concerning the blister-packaging configuration (see Attachment 1).

B. SAFETY EVALUATOR RISK ASSESSMENT

To date, the Agency has received three (3) medication error reports involving Thalomid. One medication error report involved name confusion between Thalomid and Thalitone (chlorthalidone). Unfortunately, a patient received three weeks of Thalitone 200 mg (50 mg X 4) instead of Thalomid 200 mg and experienced hypotension. Although Thalomid has been available since July 1998, only one (1) report of name confusion involving Thalomid was received by the Agency. Therefore, there is insufficient evidence at this time to conclude that the proprietary name, Thalomid, has a significant potential for name confusion. DMETS will continue to monitor post-marketing medication errors in association with the proprietary name, Thalomid.

The Agency received two medication error reports relating to the packaging of Thalomid. Currently, Thalomid is only available in blister packs of 14 and 28 capsules. The blister pack does not have the name of the drug, strength, lot number, or expiration date on the foil backing of each capsule. In one hospital, the Thalomid blister pack had been cut apart into individual doses, leaving most of the capsules without an identification of the drug, patient name, lot number, and expiration date. Another reporter also expressed concerns that sending a full card of Thalomid to a patient care unit is extremely dangerous, because it may not be labeled properly, resulting in misadministration to the wrong patient. Also, this reporter was concerned that the package design does not allow for dosing changes. At the time of initial dispensing, a card may be labeled with the dosing instructions and a subsequent dose change may follow. This could lead to errors, because the original label affixed to the blister package will have the old dosing recommendations.

DMETS recognizes the special needs of the inpatient setting. However, we have safety concerns with the introduction of unit dose strips. The availability of unit dose strips may increase the risk of a wrong patient receiving Thalomid from an inpatient setting if a Thalomid unit dose strips get placed in the wrong bin. We are especially concerned due to the availability of a drug product that sounds and looks similar to Thalomid-Thalitone. As mentioned above, the Agency has received one medication error report involving Thalomid and Thalitone name confusion. Due to the risk of severe, life-threatening human birth defects, Thalomid must not inadvertently be administered to the wrong patient. Therefore, careful consideration should be given to an alternate packaging configuration, which will accommodate an inpatient setting. The current packaging configuration should be revised so

that each blister bears the proprietary and established names, product strength, lot number, and expiration date in order to prevent further errors. Lastly, the statement, "Dispense Blister Packs Intact," appears only on the outer shipping carton. Therefore, this statement should be included on the blister card and carton as well. The placement of this statement did not prevent an incident where the Thalomid blister pack was cut apart, leaving the Thalomid capsules unidentified.

III. LABELING COMMENTS

DMETS has reviewed the blister pack labels, carton and insert labeling of Thalomid and has identified several areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENT

1. Currently, Thalomid is available in blister packs of 14 and 28 capsules and unit dose strips are not available for inpatient settings. We received a medication error report from a hospital where Thalomid blister pack had been cut apart into individual doses, leaving the remaining capsules without any identification. Due to the use of Thalomid in an inpatient setting and the extreme danger associated with Thalomid, we recommend a blister packaging that bears the proprietary and established names, product strength, lot number, and expiration date on the foil backing of each Thalomid capsule.

2. The statement, "Dispense Blister Packs Intact," appears only on the outer shipping carton. The placement of this statement did not prevent an incident where the Thalomid blister pack was cut apart, leaving the Thalomid capsules unidentified. We recommend including this statement on the carton and blister card as well.

B. CARTON LABELING (50 mg, 100 mg, and 200 mg)

1. The letter "O" should be revised to appear in the same color and font as the remaining letters of the proprietary name. Currently, the letter "O" appears in red and is designed so that it impedes the readability of the proprietary name. Presentation of the "O" makes the name appear as "THAL MID."

2. We recommend relocating the net quantity to the bottom the carton labeling in order to prevent confusion with the strength.

3. In order to prevent medication errors due to the similarity in labeling among the three strengths (50 mg, 100 mg, and 200 mg), we recommend highlighting the "strengths" with the use of contrasting color, boxing, or some other means. We also recommend increasing the prominence of the strength.

4. The statement "Dispense no more than a 4-week (28-day) supply, with no

automatic refills" is unclear. Please revise the statement to read "Thalomid prescription is NOT refillable."

C. BLISTER PACK LABELS (50 mg, 100 mg, and 200 mg)

1. See comments under **General Comments.**

2. See comments under B1, B2, and B3.

3. Revise the foil backing to include the following: proprietary and established names, product strength, lot number, and expiration date.

D. INSERT LABELING

1. DOSAGE AND ADMINISTRATION

   Please add "mg" after "100" in the statement "dosing should be initiated at 100 to 300 mg/day" to prevent dosing errors.

2. PHARMACISTS NOTE

   See comments under B4.

IV. RECOMMENDATIONS

DMETS recommends the implementation of the proposed labeling in conjunction with the labeling revisions outlined above in order to prevent the potential for medication errors.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, project manager, at 301-827-3242.

Hye-Joo Kim, Pharm.D.
Safety Evaluator
Division of Medication Error and Technical Support

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Error and Technical Support

ATTACHMENT 1

THALOMID

Source	Date of Event or Report (Location)	Description
ISR 3652414-5	1/10/2001 (Unspecified)	**Actual Error-**A Physician ordered "Thalidomide 200 mg po QHS", but a pharmacist interpreted it as "Thalitone 200 mg". The patient received 4 tablets of 50 mg Thalitone for three weeks and experienced hypotension.
ISR 3805485-7	9/25/01 (Long Beach, CA)	**Potential Error-**A pharmacist from an acute care hospital expressed concerns over the packaging of Thalomid. When a patient is admitted to this hospital, a patient receives Thalomid from a blister pack assigned specifically to that patient. Since Thalomid blister pack is not perforated to allow separation of the capsules from one another, it was expected that each dose would be removed by the nurse by pushing it through the foil, leaving the package otherwise intact and properly labeled. However, at this hospital, there was a case where the blister pack had been cut apart into individual doses, leaving most of the capsules without an identification of the drug or the patient, lot number, and expiration date. There was a potential for inadvertent administration of Thalomid to a wrong patient. The reporter requested that the manufacturer place the name of Thalomid and the strength to the foil side of the blister pack, behind each capsule to improve the safety of Thalomid use in an inpatient setting where unit-dosed medication is the norm.
ISR 3869205-2	1/28/2002 (Buffalo, NY)	**Potential Error-**A pharmacist expressed the following concerns: a) Due to the unavailability of unit doses, the potential for error is extremely high according to the reporter. Sending a full card of Thalomid to the patient care unit is extremely dangerous, because a wrong patient may receive Thalomid. Also, he is concerned that the dose may change after labeling the blister pack. b) The reporter wants to know if a patient needs to sign a consent form after each dose change; Thalomid doses are constantly adjusted in an inpatient setting. c) The hospital pharmacy is required to put the "length of therapy" in the computer system for the patient. If a patient receives an "arbitrary 30 day supply and is discharged in 7days," the reporter wants to know if the patient will be refused Thalomid prescription from an outpatient pharmacy.

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/s/

Hye-Joo Kim
7/24/02 02:05:56 PM
PHARMACIST

Carol Holquist
7/24/02 02:16:43 PM
PHARMACIST

Jerry Phillips
7/24/02 02:57:24 PM
DIRECTOR

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-785/S-021 **PRIOR APPROVAL SUPPLEMENT**

Celgene Corporation
Attention: Steve Thomas, Ph.D.
Vice President, Management and Regulatory Affairs
7 Powder Horn Drive
Warren, NJ 07059

Dear Dr. Thomas:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Thalomid® (thalidomide) Capsules, 50, 100, & 200 mg

NDA Number: 20-785

Supplement number: S-021

Date of supplement: May 24, 2002

Date of receipt: May 24, 2002

This supplemental application proposes the following changes:

- Provides draft labeling for Thalomid® (thalidomide) 50 mg, 100 mg, and 200 mg Capsules, which includes the package insert, blister pack cards, and cartons.
- In addition to the additional product information for these dosage strengths, this supplement also includes changes to the labeling to comply with Enhanced S.T.E.P.S. (System for Thalidomide Education and Prescribing Safety).

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Document Room
9201 Corporate Boulevard
Rockville, Maryland 20850

If you have any question, please call Matthew A. Bacho, Regulatory Project Manager, at (301) 827-2127.

Sincerely yours,

{See appended electronic signature page}

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and
Immunologic Drug Products
Office of Evaluation IV
Center for Drug Evaluation and Research

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/s/

Ellen Frank
8/14/02 03:01:23 PM
NDA 20-785/S-021

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-785/S-020

PRIOR APPROVAL SUPPLEMENT

Celgene Corporation
ATTN: Steve Thomas, Ph.D.
Vice President, Project Management and Regulatory Affairs
7 Powder Horn Drive
Warren, NJ 07059

Dear Dr. Thomas:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Thalomid (thalidomide)

NDA Number: 20-785

Supplement Number: 020

Date of Supplement: March 1, 2002

Date of Receipt: March 1, 2002

This supplement proposes the following changes:

- A change to a higher potency blend formulation.
- Replacement of the current marketed 50 mg capsule with a new 50 mg capsule formulation.
- Introduction of a 100 mg and a 200 mg capsule, bioequivalent to the new 50 mg capsule.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 30, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 2, 2002.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Matthew Bacho, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Ellen Frank
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NDA 20-785/S-020