



NDA 20-785/S-012, S-014

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

Dear Dr. Thomas:

Please refer to your supplemental new drug applications dated January 18, 2000 and May 17, 2000, received January 19, 2000 and May 18, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for THALOMID® (thalidomide) Tablets, 50 mg.

We acknowledge receipt of your submissions dated June 8, 2000, December 12, 2000, July 6, 2001 and August 22, 2001.

These supplemental new drug applications provide for the following changes to the THALOMID® label. The deleted text is noted by ~~strike through~~ and the added text is noted by double underline as follows:

1. The words "one month" were changed to "4 weeks" throughout the label.

2. **PRESCRIBERS Box**

- The following sentence was revised as follows:

"Two reliable forms of contraception must be used simultaneously unless continuous abstinence from ~~reproductive~~ heterosexual sexual ~~intercourse~~ contact is the chosen method."

- A sentence for male patients was added after the "**Before starting treatment**" paragraph to read:

"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."

3. In the **FEMALE PATIENTS** box, the first sentence in the fourth bullet was revised as follows:

"she has received both oral and written warnings of the risk of possible contraception failure and of the need to use two reliable forms of contraception simultaneously (see **CONTRAINDICATIONS**), unless continuous abstinence from ~~reproductive~~ heterosexual sexual contact is the chosen method."

4. In the **MALE PATIENTS** box, the fourth and fifth bullets have been revised as follows:

- he has received both oral and written warnings of the risk of possible contraception failure and of the ~~need to use barrier contraception when having sexual intercourse with women of childbearing potential, even if he has undergone successful vasectomy.~~ presence of thalidomide in semen. He has been instructed that he must always use barrier contraception (latex condom) during any sexual contact with women of childbearing potential, even if he has undergone successful vasectomy.
- he acknowledges, in writing, his understanding of these warnings and of the need for using barrier contraception (latex condom) ~~even if he has undergone successful vasectomy, during any sexual contact with women of childbearing potential, even if he has undergone successful vasectomy.~~ Sexually mature women who have not undergone a hysterectomy or who have not been post-menopausal for at least 24 consecutive months (i.e., who have had menses at any time in the preceding 24 consecutive months) are considered to be women of childbearing potential..

5. CLINICAL PHARMACOLOGY

- In the Pharmacokinetics and Drug Metabolism subsection, the Distribution subsection was revised to read:

~~It is not known whether thalidomide is present in the ejaculate of males.~~

~~The extent of plasma protein binding of thalidomide is unknown.~~

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.

6. CONTRAINDICATIONS

- The word "intercourse" was changed to "contact" in the first paragraph under Pregnancy: Category X.
- A paragraph was added and is now the next-to-the-last paragraph in this section as follows:

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.

7. WARNINGS

- The third sentence in the first paragraph concerning **Birth defects** was changed from:

~~Because it is not known whether or not thalidomide is present in the ejaculate of males receiving the drug, males receiving thalidomide must always use a latex condom when engaging in sexual activity with women of childbearing potential.~~

to:

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.

8. PRECAUTIONS

- The **Stevens-Johnson Syndrome** subsection was revised as follows:

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.

- A subsection concerning **Seizures** was added after the **Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis** subsection to read:

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.

- In the **Important Non-Thalidomide Drug Interactions Drugs That Interfere with Hormonal Contraceptives** subsection, the last sentence was revised as follows:

Therefore, women requiring treatment with one or more of these drugs must use two OTHER effective or highly effective methods of contraception or abstain from ~~reproductive~~ heterosexual sexual ~~intereourse~~ contact.

- The **Pregnancy** subsection was revised as follows:

Pregnancy Category X: See BOXED WARNING and CONTRAINDICATIONS.

Because of the known human teratogenicity of thalidomide, thalidomide is contraindicated in women who are or may become pregnant and who are not using the two required types of birth control or who are not continually abstaining from ~~reproductive~~ heterosexual sexual ~~intereourse~~ 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)] 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~~ 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.

9. ADVERSE REACTIONS

- The following sentence has been added after the first paragraph to read:

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.

10. STORAGE AND DISPENSING

- The first paragraph of the **PHARMACISTS NOTE** was revised as follows:

~~DRUG MUST ONLY BE DISPENSED IN NO MORE THAN A 1-MONTH SUPPLY AND ONLY ON PRESENTATION OF A NEW PRESCRIPTION WRITTEN WITHIN THE PREVIOUS 7 DAYS. SPECIFIC INFORMED CONSENT (copy attached as part of this package insert) AND COMPLIANCE WITH THE MANDATORY PATIENT REGISTRY AND SURVEY ARE REQUIRED FOR ALL PATIENTS (MALE AND FEMALE) PRIOR TO DISPENSING BY THE PHARMACIST.~~

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).

11. Important Information and Warnings for All Patients Taking THALOMID[®] (thalidomide)

- The first line in the **WARNING** box has been revised to read:

WARNING: SERIOUS SEVERE, LIFE-THREATENING HUMAN BIRTH DEFECTS.

- The **CONSENT FOR WOMEN** and the **CONSENT FOR MEN** have been completely revised to read:

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 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**:

<p>At least one highly effective method</p> <p>IUD</p> <p>Hormonal (birth control pills, injections, or implants)</p> <p>Tubal ligation</p> <p>Partner’s vasectomy</p>	<u>AND</u>	<p>One additional effective method</p> <p>Latex condom</p> <p>Diaphragm</p> <p>Cervical cap</p>
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- These birth control methods must be used for at least 4 weeks before starting THALOMID[®] (thalidomide) therapy, all during THALOMID[®] (thalidomide) therapy, and for at least 4 weeks after THALOMID[®] (thalidomide) therapy has stopped.
- 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, or 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 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

12. REFERENCES

- The following reference has been added and is now number 8 in the section to read:

“8. Eriksson T, Björkman S, Roth B, *et al.* 1998. Chirality. 10(3): 223-228.”

We have completed the review of these supplemental 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, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted August 22, 2001).

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 20-785/S-012, S-014." 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 Professional" 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

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 Robin Anderson, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Mark J. Goldberger, M.D., M.P.H.
Director
Division of Special Pathogen and Immunologic Drug
Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research