DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-785/S-022, S-023, S-024

Celgene Corporation
Attention: William R. Woolever
Director, Regulatory Affairs
7 Powder Horn Drive
Warren, NJ 07059

Dear Mr. Woolever:

Please refer to your supplemental new drug applications dated and received April 29, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for THALOMID® (thalidomide) Capsules, 50 mg, 100 mg and 200 mg.

We acknowledge receipt of your submissions dated October 2, 2003 and October 15, 2003.

These supplemental new drug applications provide for the following changes to the THALOMID®package insert (additions are double underlined and deletions are struckout):

1. CONTRAINDICATIONS

- The sentence "The risk to the fetus from the semen of male patients taking thalidomide is unknown" was added to the **Pregnancy:Category X** subsection.

2. **WARNINGS**

- The sentence "The risk to the fetus from the semen of male patients taking thalidomide is unknown" was added to the **Birth Defects** subsection.

- A "**Thrombotic Event**" subsection was added following the **Peripheral Neuropathy** subsection to read:

> **Thrombotic Events:**
> Thrombotic events have been reported in patients treated with THALOMID® (thalidomide). Patients with neoplastic and various inflammatory conditions being treated with THALOMID® (thalidomide) may have an increased incidence of pulmonary embolism, deep vein thrombophlebitis, thrombophlebitis, or thrombosis. It is not known if concomitant therapy with other medications including anticancer agents, are a contributing factor.

3. PRECAUTIONS

- **A "General"** subsection was added at the beginning of this section to read:

> **General:**
>
> The only type of thalidomide exposure known to result in drug associated birth defects are as a result of direct oral ingestion of thalidomide. Currently no specific data are available regarding the cutaneous absorption or inhalation of thalidomide in women of child-bearing potential and

whether these exposures may result in any birth defects. Patients should be instructed to not extensively handle or open THALOMID® (thalidomide) Capsules and to maintain storage of capsules in blister packs until ingestion. If there is contact with non-intact thalidomide capsules or the powder contents, the exposed area should be washed with soap and water.

Thalidomide has been shown to be present in the serum and semen of patients receiving thalidomide. If healthcare providers or other care givers are exposed to body fluids from patients receiving THALOMID® (thalidomide), appropriate precautions should be utilized, such as wearing gloves to prevent the potential cutaneous exposure to THALOMID® (thalidomide) or the exposed area should be washed with soap and water.

- The "**Bradycardia**" subsection was revised to read:

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

- The second sentence in the "**Laboratory Tests**" subsection was revised to read:

The test should be performed within the 24 hours prior to beginning thalidomide therapy and then weekly during the first 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.

- The following sentence was added to "**Information for Patients**" and appears as the second statement in this subsection:

Patients should be instructed to not extensively handle or open THALOMID® (thalidomide) Capsules and to maintain storage of capsules in blister packs until ingestion.

- The **"Important Non-Thalidomide Drug Interactions/*Drugs That Interfere with Hormonal Contraceptives*"** subsection was revised to read:

Drugs That Interfere with Hormonal Contraceptives: Concomitant use of HIV-protease inhibitors, griseofulvin, modafinil, pencillins, rifampin, rifabutin, phenytoin, ~~or~~ carbamazepine, or certain herbal supplements such as St. John's Wort with hormonal contraceptive agents~~,~~ may reduce the effectiveness of the contraception and up to one month after discontinuation of these concomitant therapies. 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 while taking thalidomide.

- The sentence "The risk to the fetus from the semen of male patients taking thalidomide is unknown" was added to the **Pregnancy**/***Pregnancy Category X*** subsection.

4. ADVERSE REACTIONS

- The following sentence was added to the end of the **"Other Adverse Event"** subsection:

"The use of thalidomide may not limit disease progression and/or death."

- The "**Other Adverse Events Observed in ENL Patients/Metabolic and Endocrine**" subsection was revised to read:

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.

- The "**Other Adverse Events Observed in HIV-seropositive Patients/Body As a Whole**" subsection was revised to read:

Body as a Whole: Ascites, AIDS, allergic reaction, cellulitis, chest pain, chills and fever, cyst, decreased CD4 count, facial edema, flu syndrome, hernia, thyroid hormone level altered, moniliasis, photosensitivity reaction, sarcoma, sepsis, viral infection.

- An **"Other Adverse Events Observed In Post-Marketing Use"** subsection was added following the "**Other Adverse Events Observed in HIV-seropositive Patients"** subsection to read:

Other Adverse Events Observed in Post-Marketing Use

Cardiovascular System: Cardiac arrhythmias including atrial fibrillation, bradycardia, tachycardia, sick sinus syndrome and EKG abnormalities.
Metabolic and Endocrine: Electrolyte imbalance including hypercalcemia or hypocalcemia, hyperkalemia and hypokalemia, hyponatremia, hypothyroidism, and increased alkaline phosphatase.
Nervous System: Changes in mental status or mood including depression and suicide attempts, disturbances in consciousness including lethargy, syncope, loss of consciousness or stupor, seizures including grand mal convulsions and status epilepicus.
Skin and Appendages: Erythema multiforme.
Hemic and Lymphatic: Decreased white blood cell counts including neutropenia and febrile neutropenia, changes in prothrombin time.
Respiratory System: Pleural effusion.

4. HOW SUPPLIED

- The following sentence was deleted:

~~Boxes of 140 containing 10 prescription packs of 14 capsules each (NDC 59572-105-92).~~

6. STORAGE AND DISPENSING

- The third and fourth sentences in the **PHARMACISTS NOTE** subsection were revised to read:

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. A NEW ~~SUPPLY, WITH NO AUTOMATIC RE#FILLS;~~ PRESCRIPTION IS REQUIRED FOR

FURTHER DISPENSING.

- The storage statement was revised to read:

  Store at ~~59 to 86ºF; 15 to 30ºC.~~ 25 º C (77º F); excursions permitted to 15 – 30º C (59 -86º F). [See USP Controlled Room Temperature].

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 (enclosed). 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 October 15, 2003).

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-022, S-023, S-024." 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}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug 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

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