THALOMID® (thalidomide)

Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

Contact Information:
Customer Care Center: **1-888-423-5436**
www.celgene.com

RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

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

1. GOAL

The goals of the THALOMID risk evaluation and mitigation strategy are as follows:

1. To prevent the risk of fetal exposure to THALOMID.
2. To inform prescribers, patients, and pharmacists on the serious risks and safe-use conditions for THALOMID.

2. REMS ELEMENTS

2.1. Medication Guide

A Medication Guide for THALOMID is dispensed with each prescription for THALOMID in accordance with 21 CFR 208.24, as described below.

THALOMID is packaged as a single-unit of use blister pack. The Medication Guide (MG) is included as part of the Prescribing Information for THALOMID (PI), and separated by perforations. This PI/MG combination is inserted in the pocket of the blister card and this entire unit is dispensed to the patient for each prescription. As the MG is included as part of the primary blister pack for THALOMID, Celgene is ensured that every patient receives a MG with each prescription.

Please see the appended Medication Guide.

2.2. Elements to Assure Safe Use

2.2.1. Healthcare providers who prescribe THALOMID® are specially certified in the *S.T.E.P.S.*® program with Celgene:

Celgene will ensure that healthcare providers who prescribe THALOMID are specially certified in the *S.T.E.P.S.* program. To become certified, each prescriber must complete the Prescriber Registration Form and agree to do the following:

a. Provide patient counseling on the benefits and risks of THALOMID therapy, including the risks described in the BOXED WARNINGS.

b. Complete and submit to the Celgene Customer Care Center a signed Patient-Physician Agreement Form (PPAF) via fax, identifying the patient's risk category (see PPAFs for all six risk categories) for each new patient. In signing the PPAF, each prescriber acknowledges that they understand that THALOMID is available only through the *S.T.E.P.S.* Program, and that they must comply with program requirements.

c. Provide contraception and emergency contraception counseling with each new prescription prior to and during THALOMID treatment.

d. Provide scheduled pregnancy testing for females of childbearing potential and verify negative pregnancy test results prior to writing a new prescription or subsequent prescriptions.

e. Report any pregnancies in female patients or female partners of male patients prescribed THALOMID immediately to Celgene Drug Safety (or Celgene Customer Care Center).

f. Complete a prescriber survey for every patient (new and follow-up), obtain a new authorization number for each prescription written, and include this authorization number on every prescription.

g. Facilitate compliance with a mandatory *S.T.E.P.S.* patient monitoring telephone survey by instructing patients to complete the mandatory surveys at program specified frequencies.

h. Prescribe no more than a 4-week (28-day) supply, with no automatic refills or telephone prescriptions.

i. Return all unused THALOMID brought in by patients to Celgene Customer Care.

j. Re-register patients in the *S.T.E.P.S.* Program if THALOMID is required and previous therapy with THALOMID has been discontinued for 12 consecutive months.

Celgene will:

1. Maintain a secure database of all certified prescribers in the *S.T.E.P.S.* Program.
2. Monitor to ensure that only certified prescribers are prescribing THALOMID.
3. Monitor and ensure that patients have been assigned correctly to one of the following patient risk categories. Confirm risk category when completing the PPAFs during the patient registration process:
    a. **Adult female of childbearing potential:** all females who are menstruating, amenorrheic from previous medical treatments, under 50 years, and/or perimenopausal.
    b. **Female child of childbearing potential:** all females under 18 years who are menstruating.

c. **Adult female NOT of childbearing potential:** females who have had a natural menopause for at least 24 consecutive months, a hysterectomy, and/or bilateral oopherectomy.

d. **Female child NOT of childbearing potential:** all females under 18 years who are not menstruating.

e. **Adult males 18 years or older**

f. **Male child under 18 years**

4. Monitor certified prescriber compliance with the *S.T.E.P.S* .Program, including patient risk categorization and the appropriate corresponding counseling requirements, contraception requirements, pregnancy testing, and survey completion for all patients treated with THALOMID.
5. Institute corrective action and prevent the certified prescriber from prescribing THALOMID if the prescriber is found to be non-compliant with the *S.T.E.P.S.* Program.
6. Train *S.T.E.P.S.* Program certified prescribers in adverse experience reporting procedures, including the requirement to immediately report to Celgene any suspected fetal exposure to THALOMID if a pregnancy occurs, by providing to the prescriber the "Healthcare Professional Adverse Drug Experience Reporting Procedure".
7. Ensure that once the prescriber submits the completed PPAF, the prescriber will receive a confirmation letter via fax to confirm the patient's enrollment and signify that the prescriber and patient telephone surveys can be taken to receive an authorization number for the THALOMID prescription (for all males, the PPAF is considered the initial telephone survey). The authorization number is written on the THALOMID prescription
8. Ensure that, for subsequent prescriptions, the prescriber completes a telephone survey designed to look for signals of at-risk behavior (e.g., pending or outdated pregnancy test), report the patient's pregnancy test results, correct assignment of risk category, and confirm or re-enforce patient understanding of contraceptive requirements. The completion of the monthly survey will allow the prescriber to obtain a new authorization number every time a prescription for THALOMID is written.

The following appended materials are part of the REMS:

1) Prescriber Registration Form
2) Patient-Physician Agreement Form (PPAF)
3) Patient Registration Application Software and User Guides
4) Program Overview (*S.T.E.P.S.*® At-A-Glance)
5) *S.T.E.P.S.*® Prescriber Guide to English and non-English Materials
6) *S.T.E.P.S.*® Instructions for Providers
7) *S.T.E.P.S.*® Patient Resource Pack

8) Healthcare Professional Adverse Drug Experience Reporting Procedure

2.2.2. THALOMID will be dispensed only by pharmacies that are specially certified in the *S.T.E.P.S.* Program:

Celgene will ensure that THALOMID is only dispensed from certified pharmacies. To become a *S.T.E.P.S.* Program certified pharmacy, the head pharmacist or director of pharmacy will complete the Pharmacy Registration Form and will agree to do the following before filling a THALOMID prescription:

a. Verify all prescriptions have an authorization number. All authorization numbers are valid for 7 days. Telephone prescriptions are not permitted. Faxed prescriptions may be permissible depending on state laws.

b. Call each unique authorization number into the automated system at the Celgene Customer Care Center and obtain a confirmation number, using the following procedure:

1. Enter the pharmacy identification number (NABP or DEA);
2. Enter the authorization number written on the prescription;
3. Enter the number of capsules and milligram (mg) strength being dispensed;
4. Obtain a confirmation number through the Interactive Voice Response (IVR) system or through a Customer Care Center Representative, and write this number on the prescription.
5. Dispense or ship the prescribed THALOMID within 24 hours of obtaining and recording the confirmation number.

c. Dispense no more than a 4-week (28-day) supply, along with the Medication Guide and require a new prescription from the patient prior to dispensing additional THALOMID.

d. Dispense subsequent prescriptions only if fewer than 7 days of therapy remain on the previous prescription.

e. Dispense blister packs intact; capsules cannot be repackaged.

f. Not to redistribute or transfer THALOMID between pharmacies.

g. Educate all staff pharmacists dispensing THALOMID about the dispensing procedure for THALOMID.

The following appended materials are part of the REMS:

1. Pharmacy registration form
2. Guidelines for Dispensing/Ordering THALOMID (thalidomide) Capsules

2.2.3. THALOMID will only be dispensed to patients enrolled in the *S.T.E.P.S.* Program with evidence or other documentation of safe use conditions.

Celgene will ensure that all patients treated with THALOMID are enrolled in the *S.T.E.P.S.* Program by a registered prescriber and that each patient and/or guardian of underage patients consents to participate in the program by:

a. acknowledging that he or she understands that:
   i. severe birth defects or death to an unborn baby may occur if a female becomes pregnant while she is receiving THALOMID;
   ii. THALOMID must not be shared with anyone, even someone with similar symptoms;
   iii. THALOMID must be kept out of the reach of children and should NEVER be shared with females who are able to have children;
   iv. they cannot donate blood while receiving THALOMID;
   v. they might be asked to participate in the THALOMID Pregnancy Exposure Registry;
   vi. they will be asked to participate in an additional voluntary survey about the REMS; and
   vii. they may be contacted by Celgene about following the rules of the REMS.

b. In addition, each patient and/or guardian of underage patients consents to participate in the program by:
   i. agreeing to return unused THALOMID to Celgene;
   ii. agreeing to participate in a monthly telephone survey while on THALOMID (with the exception of Adult Females Not of Childbearing Potential who are required to take a survey once every six months); and
   iii. reviewing the *S.T.E.P.S.* Program educational materials and Medication Guide and asking their prescriber any questions that have not been answered.

In addition, **Females and guardians of underage females** must attest to their understanding of their/their child's childbearing potential, as categorized by the prescribing physician.

Females of childbearing potential (FCBP) and guardians of underage FCBP will attest that they/their child:

a. is not currently pregnant, and will try to refrain from becoming pregnant while receiving THALOMID therapy, during dose interruptions, and for at least 4 weeks after completely stopping THALOMID therapy;
b. must not take THALOMID if pregnant, breastfeeding a baby, or not using birth control as defined in the REMS;
c. will, unless abstinent, use contraception as defined within the REMS: for 4 weeks before starting THALOMID, while receiving THALOMID, during dose interruptions, and for at least 4 weeks after stopping THALOMID;

d. will have pregnancy testing done as ordered by the certified prescriber 24 hours prior to starting THALOMID, every week for the first 4 weeks of THALOMID therapy, and then every 4 weeks if the FCBP has regular menstrual cycles, or every 2 weeks if the FCBP has irregular menstrual cycles, while receiving THALOMID;

e. will immediately stop taking THALOIMID and inform the certified prescriber if the patient becomes pregnant, misses a menstrual period, experiences unusual menstrual bleeding, stops using contraception, or thinks for any reason that she might be pregnant; if the prescriber is not available, the FCBP or guardian of an underage FCBP can call Celgene Drug Safety via 1-888-423-5436 or 1-888-668-2528 for information on emergency contraception.

Males or Guardians of males will attest that they/their child will:

a. never have unprotected sexual contact with a woman who can become pregnant;

b. wear a latex condom every time the male patient has sexual contact with a woman who is or who can become pregnant; continue condom use with sexual contact while the male patient is receiving THALOMID treatment and for 4 weeks after the male patient stops taking THALOMID, even if the patient has had a successful vasectomy;

c. inform their certified prescriber if the male patient has unprotected sexual contact with a woman who can become pregnant, or if they think for any reason that the male patient's sexual partner might be pregnant; the male patient or guardian of an underage male patient can call Celgene Drug Safety via 1-888-423-5436 or 1-888-668-2528 for information on emergency contraception.

d. will not donate sperm while taking and for 4 weeks after stopping THALOMID.

Celgene will ensure that a completed PPAF is submitted via fax for each patient who receives THALOMID.

The following appended materials are part of the REMS:

1) Patient Resource Pack including Important Information for Men and Women Taking THALOMID
2) Patient Registration and Patient-Physician Agreement Form Adult Male
3) Patient Registration and Patient-Physician Agreement Form for Male Child
4) Patient Registration and Patient-Physician Agreement Form for Adult Female NOT of Childbearing Potential
5) Patient Registration and Patient-Physician Agreement Form for Adult Female of Childbearing Potential
6) Patient Registration and Patient-Physician Agreement Form for a Female Child NOT of Childbearing Potential
7) Patient Registration and Patient-Physician Agreement Form for a Female Child of Childbearing Potential

2.2.4. Female patients or female partners of male patients receiving THALOMID who report a pregnancy that occurred during THALOMID therapy will be enrolled in a THALOMID Pregnancy Exposure Registry. The registry will collect the following information:

Upon receiving a report of pregnancy from the *S.T.E.P.S.* program, Celgene Pregnancy Prevention Plan programs in the rest of the world, clinical trials, or directly from a prescriber or patient, Celgene will enroll the female patient or female partner of the male patient taking THALOMID into the THALOMID Pregnancy Exposure Registry. The objectives of the registry are to monitor pregnancy outcomes in female patients of childbearing potential and male patients' female partners who are exposed to THALOMID and to understand why the *S.T.E.P.S.* program was unsuccessful.

The following materials are part of the REMS and are appended:

1) *S.T.E.P.S.* Pregnancy Exposure Registry Protocol, including letter and questionnaires

2.3. Implementation System

The implementation system will include the following:

1.) Celgene will maintain a secure database of all certified entities, including enrolled patients and dispensing entities (retail, hospital, and specialty pharmacies) to monitor and evaluate implementation of the elements provided for in Sections 2.2.3 and 2.2.4.

2.) Celgene will monitor distribution of THALOMID to determine whether the drug is only shipped to certified dispensing entities and patients.

3.) Celgene will monitor *S.T.E.P.S.* program pharmacy compliance and address deviations by monitoring real time dispensing activity and conducting pharmacy audits.

a. The Celgene Customer Care Center will monitor the certified pharmacies in the manner described in the REMS supporting document to ensure only enrolled and authorized patients are receiving THALOMID. If a certified pharmacy is found to be non-compliant with the *S.T.E.P.S.* program, Celgene will institute corrective action and may de-activate pharmacies for which re-training has proven ineffective, removing them from the *S.T.E.P.S.* program.

b. Celgene will perform regular on-site audits of a sampling of pharmacies participating in the *S.T.E.P.S.* program. The sampling will cover retail, specialty, and hospital pharmacies. The compliance information gathered from these audits together with real time compliance information collected by the Celgene Customer Care Center will be used to develop a risk-based assessment tool to select which pharmacies are to be audited. The *S.T.E.P.S.* compliance audits will be performed by internal auditors of Celgene and/or outside auditors contracted and trained by Celgene—the auditors are independent of every other organization responsible for the sales of THALOMID or the effective operations of the *S.T.E.P.S.* progam.

4.) The Celgene Customer Care Center will address customer complaints received that are related to the *S.T.E.P.S.* process and distribution and dispensing of THALOMID. With the "real-time" intervention of the Risk Management Intervention Specialist, most issues are addressed within one day.

5.) Celgene will monitor and ensure that the prescriptions are filled within the allowed timeframes.

6.) Celgene will maintain a reporting and collection system for safety information that includes a process to monitor pregnancy testing results and pregnancy outcomes (should one occur) through the S.T.E.P.S. Pregnancy Registry and to understand why the *S.T.E.P.S.* program was unsuccessful for the pregnancy case in question.

7.) Based on monitoring and evaluation of these Elements to Assure Safe Use, Celgene will take reasonable steps to work to improve implementation of these elements, as applicable.

8.) Celgene will develop and follow written procedures related to the implementation of the REMS.

2.4. Timetable for Submission of Assessment Reports

REMS assessments (*S.T.E.P.S.* ® update reports) will be submitted at 1 year post REMS approval, then every 3 years thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. Celgene will submit each assessment so it will be received by the FDA on or before the due date.

MEDICATION GUIDE

THALOMID (tha-lo-mid) -

(thalidomide) -

Capsules -

Read the Medication Guide that comes with THALOMID before you start taking it and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about THALOMID?

- Before you begin taking THALOMID, you must read and agree to all of the instructions in the *S.T.E.P.S.® program.*
- THALOMID can cause serious side effects including:

  Major birth defects (deformed babies) or death of an unborn baby. Females who are pregnant or who plan to become pregnant must not take THALOMID. THALOMID can cause serious side effects including severe, life-threatening human birth defects. Females must not become pregnant:

  - for 4 weeks before starting THALOMID
  - while taking THALOMID
  - during any breaks (interruptions) in your treatment with THALOMID
  - for 4 weeks after stopping THALOMID

  If you become pregnant while taking THALOMID, stop taking it right away and call your healthcare provider. If your healthcare provider is not available, you can call 1-888-668-2528 for medical information. Healthcare providers and patients should report all pregnancies to:

  - FDA MedWatch at 1-800-FDA-1088, and -
  - Celgene Corporation at 1-888-423-5436

  Males should know that THALOMID passes into semen or sperm.

  - Males, including those who have had a vasectomy, must use a latex condom during any sexual contact with a pregnant female or a female that can become pregnant, while taking THALOMID, during any breaks (interruptions) in your treatment, and for 4 weeks after stopping THALOMID. (If you or your partner is allergic to latex, please consult with your healthcare provider.)
  - Do not have unprotected sexual contact with a female who is or could become pregnant. Tell your healthcare provider if you do have unprotected sexual contact with a female who is or could become pregnant.
  - Do not donate sperm while taking THALOMID, during any breaks (interruptions) in your treatment, and for 4 weeks after stopping THALOMID. If

a female becomes pregnant with your sperm, the baby may be exposed to THALOMID and may be born with birth defects.

Men, if your female partner becomes pregnant, you should call your healthcare provider right away.

A higher chance for blood clots in your veins and lungs. Ask your healthcare provider about whether you should take aspirin or other medicines that can potentially prevent blood clotting. Call your healthcare provider or get medical help right away if you get any of these signs or symptoms:

- shortness of breath -
- chest pain -
- arm or leg swelling

What is THALOMID?

THALOMID is a prescription medicine taken, with the medicine dexamethasone, to treat people who have been newly diagnosed with multiple myeloma. Multiple myeloma is a cancer of plasma cells. Plasma cells are found in the bone marrow. Normal plasma cells produce proteins called antibodies. Some antibodies can attack and kill disease-causing germs. People with multiple myeloma may have low blood cell counts and immune problems, giving them a higher chance for getting infections such as pneumonia. They may also have bone pain and breaks (fractures).

THALOMID is also used to treat people when new lesions of leprosy flare up. THALOMID is not used by itself to treat the skin lesions when there is moderate to severe nerve pain. THALOMID is used as a treatment to keep the lesions in check or to prevent the skin lesions of leprosy from coming back (recurring).

Who should not take THALOMID?

- **Do not take THALOMID if you are pregnant, plan to become pregnant, or become pregnant during THALOMID treatment.** See "What is the most important information I should know about THALOMID?"
- **Do not take THALOMID if you are allergic to anything in it.** See the end of this Medication Guide for a complete list of ingredients in THALOMID.

What should I tell my healthcare provider before taking THALOMID?

Tell your healthcare provider about all of your medical conditions, including if you:

- **are pregnant or breastfeeding.** THALOMID must not be used by women who are pregnant or breastfeeding. See "What is the most important information I should know about THALOMID?" It is not known if THALOMID passes into your breast milk and harms your baby. -

Tell your healthcare provider about all the medicines you take including prescription and non prescription medicines, vitamins, and herbal supplements. THALOMID and other medicines may affect each other causing serious side effects.

Certain medicines can affect the way that birth control pills, injections, patches, or implants work. You could become pregnant. Especially tell your healthcare provider if you also take:

- a penicillin antibiotic
- an anti-HIV medicine
- phenytoin (Fosphenytoin, Cerebyx, Dilantin-125, Extended Phenytoin Sodium, Prompt Phenytoin Sodium, Phenytek, Dilantin, Phenytoin Sodium
- carbamazepine (Carbatrol, Equetro, Tegretol, Tegretol-XR, Teril, Epitol
- rifampin (Rifater, Rifamate, Rimactane, Rifadin)
- the herbal supplement St. John's Wort
- modafinil (Nuvigil, Provigil)
- griseofulvin (Grifulvin V, Gris-Peg)

Also see the patient brochure called "Important Information for Men and Women Taking Thalomid."

Ask your healthcare provider if you are not sure if your medicine is one of these.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist.

How should I take THALOMID?

Take THALOMID exactly as prescribed and follow all the instructions of the *S.T.E.P.S.* program. Before prescribing THALOMID, your healthcare provider will:

- explain the *S.T.E.P.S.* program to you
- have you sign the Patient-Physician Agreement Form
- Keep THALOMID in the blister pack until you take your daily dose.
- Swallow THALOMID capsules whole with water.
- THALOMID is taken one time each day, at least 1 hour after your evening meal. Bedtime is the preferred time to take THALOMID.
- Do not open the THALOMID capsules or handle them any more than needed. If you touch a broken THALOMID capsule or the medicine in the capsule, wash the area of your body with soap and water.
- If you miss a dose of THALOMID and it has been less than 12 hours since your regular time, take it as soon as you remember. If it has been more than 12 hours, just skip your missed dose. Do **not** take 2 doses at the same time.
- If you take too much THALOMID or overdose, call your healthcare provider or poison control center right away.

Females who can become pregnant:

- will have pregnancy tests weekly for 4 weeks, then every 4 weeks if your menstrual cycle is regular, or every 2 weeks if your menstrual cycle is irregular.

  If you miss your period or have unusual bleeding, you will need to have a pregnancy test and receive counseling.

- must agree to use 2 different forms of effective birth control at the same time, for 4 weeks before, while taking, during any breaks (interruptions) in your treatment, and for 4 weeks after stopping THALOMID.

Males who take THALOMID, even those who have had a vasectomy, must agree to use a latex condom during sexual contact with a pregnant female or a female who can become pregnant. (If you or your partner is allergic to latex, please consult with your healthcare provider.)

What should I avoid while taking THALOMID?

- **Females: Do not get pregnant and do not breastfeed while taking THALOMID.**

  Males: Do not donate sperm. See "What is the most important information I should know about THALOMID?, Who should not take THALOMID?, and What should I avoid while taking THALOMID?"

- **Do not share THALOMID® with other people.** It may cause birth defects and other serious problems.
- **Do not donate blood** while you take THALOMID, during any breaks (interruptions) in your treatment, and for 4 weeks after stopping THALOMID. If someone who is pregnant gets your donated blood, her baby may be exposed to THALOMID and may be born with birth defects.
- THALOMID can cause dizziness and drowsiness. Avoid drinking alcohol, operating machinery, and driving a car when taking THALOMID. Avoid taking other medicines that may cause drowsiness without talking to your healthcare provider first.

What are the possible side effects of THALOMID?

THALOMID may cause serious side effects:

- See "What is the most important information I should know about THALOMID?"

THALOMID can also cause the following other side effects:

- **Drowsiness and sleepiness**. See "What should I avoid while taking THALOMID?"
- **Nerve damage.** Nerve damage is common with THALOMID. If the nerve damage is severe, it may not go away. Stop taking THALOMID and call your healthcare provider right away if you have any of these early symptoms of nerve damage in your hands, legs, or feet:
  - numbness
  - tingling
  - pain
  - burning sensation
- **Dizziness and decreased blood pressure when changing positions**. THALOMID may cause a decrease in your blood pressure, and you may feel dizzy when you go from a lying down or sitting position to standing up. When changing positions, sit upright for a few minutes before standing to help prevent this.
- **Decreased white blood cell count.** THALOMID can cause decreased white blood cell counts, including neutrophils. Neutrophils are a type of white blood cell that is important in fighting bacterial infections. Your healthcare provider should check your white blood count before and regularly while you take THALOMID. If your neutrophils are too low you should

not start THALOMID and if they are low during treatment, your dose of THALOMID may need to be changed.

- **Increased HIV virus in the blood.** If you are HIV positive, your healthcare provider will check your blood tests for this problem after one month and three months of treatment, then every 3 months after that.
- **Allergic reaction**. Allergic reactions can happen with THALOMID and may be severe. Call your healthcare provider or get medical help right away if you have any of these symptoms of allergic reaction:
    - a red, itchy rash -
    - fever -
    - fast heartbeat -
    - feel dizzy or faint -
- **Slow heartbeat (bradycardia)**. Tell your healthcare provider if this is a problem for you. Report specific symptoms, such as fainting, dizziness or shortness of breath, to your healthcare provider.
- **Serious skin reactions**. Serious skin reactions can happen with THALOMID and may cause death. Call your healthcare provider right away if you have any skin reaction while taking THALOMID.
- **Seizures**. Tell your healthcare provider right away if you have a seizure while taking THALOMID.

Common side effects of THALOMID include:

- tiredness -
- tremor -
- swelling of the hands and feet -
- constipation -
- rash -
- dizziness -

These are not all the possible side effects of THALOMID. Tell your healthcare provider about any side effect that bothers you or that does not go away.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store THALOMID?

- Store THALOMID at room temperature, between 59°F to 86°F (15°C to 30°C). Protect from light.

Keep THALOMID and all medicines out of the reach of children.

General information about THALOMID

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Do not** take THALOMID for conditions for which it was not prescribed. **Do not** give

THALOMID to other people, even if they have the same symptoms you have. It may harm them and may cause birth defects.

This Medication Guide provides a summary of the most important information about THALOMID. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about THALOMID that is written for healthcare professionals. You can also call 1-888-423-5436 or visit www.THALOMID.com.

What are the ingredients in THALOMID?

Active ingredient: thalidomide

Inactive ingredients: 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 150 mg capsule shell contains FD&C blue #2, black iron oxide, yellow iron oxide, titanium dioxide, gelatin, and black and white ink. The 200 mg capsule shell contains FD&C blue #2, titanium dioxide, gelatin, and white ink.

Manufactured for Celgene Corporation

Summit, NJ 07901

This Medication Guide has been approved by the U.S. Food and Drug Administration.

ThalPlyMG.00 0X/09

Celgene Corporation
86 Morris Avenue
Summit, New Jersey 07901

1-888-423-5436 • www.THALOMID.com

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To generate the appropriate Patient Registration/Patient-Physician Agreement Form, please refer to the instructions included for installing and using this program. Software only needs to be installed once.

THALOMID®
(thalidomide) Capsules

Patient Registration Application Software and User Guides

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

S.T.E.P.S.® At-A-Glance

Initial Prescription

1. Counsel and perform pregnancy testing (if applicable)
2. Provide mandatory counseling: no drug sharing, no blood or sperm donation, and appropriate contraception. Patients should be instructed to not extensively handle or open THALOMID® (thalidomide) Capsules and to maintain storage of capsules in blister packs until ingestion
3. Complete, print, and sign Patient Registration/ Patient-Physician Agreement Form
   - **Males (adults and children)**
   - **Females of childbearing potential include females who have not undergone a natural menopause** for at least 24 months
   - **Adult females not of childbearing potential include females who have had a natural menopause** for more than 24 consecutive months, a hysterectomy, or bilateral oophorectomy
4. Fax Patient Registration/Patient-Physician Agreement Form to 1-888-432-9325
5. Instruct patient to complete phone survey by calling 1-888-423-5436 prior to prescriber obtaining an authorization number
   - **All males:** Patient Registration/Patient-Physician Agreement Form is considered the initial phone survey
   - **All females:** Complete the appropriate phone survey
6. Complete a prescriber phone survey by calling 1-888-423-5436, and obtain a new authorization number for each prescription
   - You will need to enter the following information:
     - Prescriber's DEA number or Social Security number
     - Patient's Social Security number
     - Date and result of patient's last pregnancy test (if applicable); valid only for 7 days
     - Average daily dose
     - Total number of days supplied (cannot exceed 28 days)
7. Write the authorization number on the prescription; prescription and authorization number are valid only for 7 days
8. If drug is not dispensed within 7 days, surveys must be repeated. To cancel authorization number(s), call 1-888-423-5436

Subsequent Prescriptions

1. Perform scheduled pregnancy testing (if applicable)
2. Provide mandatory counseling: no drug sharing, no blood or sperm donation, and appropriate contraception. Patients should be instructed to not extensively handle or open THALOMID® (thalidomide) Capsules and to maintain storage of capsules in blister packs until ingestion
3. Instruct patient to complete surveys **as scheduled**, prior to prescriber obtaining an authorization number and filling prescription
   - Monthly:
     - **Males (adults and children)**
     - **Females of childbearing potential (adults and children), female children not of childbearing potential**
   - Every 6 months:
     - **Adult females not of childbearing potential** (if had **natural menopause** for more than 24 consecutive months, a hysterectomy, or bilateral oophorectomy)
4. Complete a prescriber phone survey, which should be done on the day the prescription is written
   - You will need to enter the following information:
     - Prescriber's DEA number or Social Security number
     - Patient's Social Security number
     - Date and result of patient's last pregnancy test (if applicable); valid only for 7 days
     - Average daily dose
     - Total number of days supplied (cannot exceed 28 days)
5. Obtain authorization number for each new prescription; faxed prescriptions are permissible if state law allows
6. Write the authorization number on the new prescription; prescription and authorization number are valid only for 7 days
7. If drug is not dispensed within 7 days, surveys must be repeated. To cancel authorization number(s), call 1-888-423-5436

Please see full Prescribing Information, including Boxed WARNINGS, CONTRAINDICATIONS, PRECAUTIONS, and ADVERSE EVENTS, enclosed in pocket.

THALOMID® (thalidomide) Capsules

Celgen

For further information about THALOMID®, please call the Celgene Customer Care Center at 1-888-423-5436 or visit www.THALOMID.com

Please see full Prescribing Information, including Boxed WARNINGS, CONTRAINDICATIONS, PRECAUTIONS, and ADVERSE REACTIONS, enclosed in pocket.

S.T.E.P.S.® program by prescribers, pharmacists, and patients registered with *S.T.E.P.S.*®. Patients should be instructed to not extensively handle or open blister packs until ingestion. THALOMID must be administered in compliance with all of the terms outlined in the

Hypersensitivity: THALOMID® (thalidomide) is contraindicated in any patients who have demonstrated hypersensitivity to the drug or its components.

Nursing mothers: It is not known whether THALOMID® (thalidomide) is excreted in human milk. Because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Peripheral neuropathy: THALOMID® (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.

Other most common adverse events: Multiple Myeloma (THALOMID®/dexamethasone): The most frequently reported adverse events were constipation (55%), sensory neuropathy (54%), confusion (28%), hypocalcemia (72%), edema (57%), dyspnea (42%), thrombosis/embolism (23%), and rash/desquamation (30%) (occurring in ≥20% of patients and with a frequency ≥10% in patients treated with THALOMID®/dexamethasone compared with dexamethasone alone). **ENL (THALOMID®):** The most frequently reported adverse events were somnolence (38%), rash (21%), headache (13%), asthenia (8%), impotence (8%), malaise (8%), pain (8%), pruritus (8%), and vertigo (8%) (occurring in ≥5% of patients). In placebo-controlled clinical trials of HIV-seropositive patient populations, there have been reports of increased plasma HIV RNA levels.

Multiple Myeloma

THALOMID® (thalidomide) in combination with dexamethasone is indicated for the treatment of patients with newly diagnosed multiple myeloma.

The effectiveness of THALOMID® (thalidomide) is based on response rates (**see CLINICAL STUDIES section**). There are no controlled trials demonstrating a clinical benefit, such as an improvement in survival.

Erythema Nodosum Leprosum

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.

WARNINGS:

1. 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 (REGARDLESS OF STRENGTH)] 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.

2. VENOUS THROMBOEMBOLIC EVENTS.

THE USE OF THALOMID® (thalidomide) IN MULTIPLE MYELOMA RESULTS IN AN INCREASED RISK OF VENOUS THROMBOEMBOLIC EVENTS, SUCH AS DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLUS. THIS RISK INCREASES SIGNIFICANTLY WHEN THALIDOMIDE IS USED IN COMBINATION WITH STANDARD CHEMOTHERAPEUTIC AGENTS INCLUDING DEXAMETHASONE. IN ONE CONTROLLED TRIAL, THE RATE OF VENOUS THROMBOEMBOLIC EVENTS WAS 22.9% IN PATIENTS RECEIVING THALIDOMIDE IN COMBINATION WITH DEXAMETHASONE COMPARED TO 4.9% IN PATIENTS RECEIVING DEXAMETHASONE ALONE ($P=0.002$). PATIENTS AND PHYSICIANS ARE ADVISED TO BE OBSERVANT FOR THE SIGNS AND SYMPTOMS OF THROMBOEMBOLISM. PATIENTS SHOULD BE INSTRUCTED TO SEEK MEDICAL CARE IF THEY DEVELOP SYMPTOMS SUCH AS SHORTNESS OF BREATH, CHEST PAIN, OR ARM OR LEG SWELLING. PRELIMINARY DATA SUGGEST THAT PATIENTS WHO ARE APPROPRIATE CANDIDATES MAY BENEFIT FROM CONCURRENT PROPHYLACTIC ANTICOAGULATION OR ASPIRIN TREATMENT.

IMPORTANT SAFETY INFORMATION

Prescriber Guide to English and Non-English Materials

Call 1-888-423-5436

- For prescribers who do not have access to a computer or whose computer systems are not compatible with the Windows®/Macintosh® CD-ROM provided with *S.T.E.P.S.*® program materials
- In 16 languages, to meet patient needs:
  – Patient Registration/Patient-Physician Agreement Forms
  – Patient Brochure
  – Survey Forms
- Instructions in English for prescribers

Available languages:

Arabic
Cambodian
Chinese
English
French
German
Greek
Italian
Japanese
Korean
Laotian
Polish
Portuguese
Russian
Spanish
Vietnamese

Patient-Physician Agreement Forms, Patient Brochure, and Survey Forms requested will be faxed directly to the number you indicate. Please be prepared to provide:

- Prescriber's
  – Name
  – DEA or Social Security number
  – Full address
- Patient's
  – Name
  – Full address
  – Phone number
  – Date of birth
  – Social Security number
  – Diagnosis (ICD-9 Code)

For female patients, you will need to provide information on whether the patient has had a surgical menopause, chemical menopause, or a natural menopause for at least 24 months.

With this information, the Celgene Customer Care Center will generate the applicable form(s) and have them faxed to the number you request.

THALOMID® (thalidomide) Capsules

1-888-423-5436 • www.THALOMID.com

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Instructions for Prescribers

Review the *S.T.E.P.S.*® Starter Kit

S.T.E.P.S.® Prescriber Resources (1 per registered prescriber)

- CD-ROM to generate Patient Registration/Patient-Physician Agreement Forms (for Windows® and Macintosh®)
- *S.T.E.P.S.*® At-A-Glance
- Prescriber Guide to English and Non-English Materials
- Instructions for Prescribers
- THALOMID® (thalidomide) Patient Chart Sticker for each chart (located on Patient Resource Pack)
- Full Prescribing Information for THALOMID® (thalidomide)

S.T.E.P.S.® Patient Resource Pack (1 per patient)

- *S.T.E.P.S.*® Guide to Patient Surveys
- Important Information for Men and Women Taking THALOMID® (thalidomide) Brochure
- Emergency Contraception Brochure
- Your Contraceptive Choices Brochure

S.T.E.P.S.® System Setup for Prescribers

- Insert appropriate computer software (CD-ROM)
- Install *S.T.E.P.S.*® Patient Registration/Patient-Physician Agreement Form Program
- Computer software is installed only once

Patient Registration

Before a patient can receive THALOMID® (thalidomide), he or she must understand and, along with the prescriber, sign a completed Patient Registration/Patient-Physician Agreement Form (available on CD-ROM).

Prescribers who do not have access to a computer or whose computer systems are not compatible with the Windows®/Macintosh® CD-ROM provided with *S.T.E.P.S.*® materials should use the Prescriber Guide to English and Non-English Materials. These services provide Patient Registration/Patient-Physician Agreement Forms, Patient Brochures, and Survey Forms in 16 languages, including English.

THALOMID®
(thalidomide) Capsules

Celgene

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Patient Registration (continued)

- Generate appropriate Patient Registration/Patient-Physician Agreement Form
  - Enter patient data
  - Enter prescriber data

- Print and complete the Patient Registration/Patient-Physician Agreement Form
  - Patient, parent/legal guardian, and/or authorized representative must read the Patient Registration/Patient-Physician Agreement Form in the language of their choice (available in 16 languages through the Celgene Customer Care Center at 1-888-423-5436)
  - **Each statement must be initialed by the patient to indicate understanding**
  - **The form must be completed and signed by both prescriber and patient**
  - If the patient is under 18 years of age, his or her legal guardian must read this material, initial the statements, sign the form, and agree to ensure compliance
  - For an incompetent adult patient, an authorized representative must sign the Patient Registration/Patient-Physician Agreement Form. An authorized representative is a caretaker authorized under applicable state law to consent to treatment on the incompetent patient's behalf. The authorized representative must read the material, initial the statements, sign the form, and agree to ensure compliance.

    Along with the Patient Registration/Patient-Physician Agreement Form, **a signed and dated letter from the prescriber, on the prescriber's letterhead, must be submitted to the Celgene Customer Care Center.** This letter must contain the following: A statement that the incompetent patient lacks the capacity to complete the Patient Registration/Patient-Physician Agreement Form, including identification of the medical condition causing the incapacity; the name and address of the authorized representative; the authorized representative's relationship to the patient; and an opinion that the authorized representative accepts responsibility for the patient's compliance with *S.T.E.P.S.*® and is authorized to consent to THALOMID® (thalidomide) treatment on behalf of the patient
  - **Do not write on Patient-Physician Agreement Form except in designated boxes**

- Fax the completed Patient Registration/Patient-Physician Agreement Form to the Celgene Customer Care Center at 1-888-432-9325

- A confirmation letter stating that surveys can be taken as required will be faxed to your office once the patient is registered. In the event that you do not receive this confirmation letter, call the Celgene Customer Care Center at 1-888-423-5436

Note: If THALOMID® (thalidomide) therapy is discontinued for 12 consecutive months, the patient must register again in the *S.T.E.P.S.*® program. Follow the above procedures to reregister the patient.

Initial THALOMID® (thalidomide) Prescriptions

After the appropriateness of THALOMID® (thalidomide) therapy has been established, please refer to the following step-by-step guidelines:

- Provide comprehensive counseling on the benefits and risks of THALOMID® (thalidomide) therapy
  - Patients must be counseled on the risks of birth defects, venous thromboembolic events, other side effects, and important precautions associated with THALOMID® (thalidomide)

Female Patients

Two categories:

1 – Females not of childbearing potential include females who have had a natural menopause for at least 24 consecutive months, a hysterectomy, and/or bilateral oophorectomy

2 – Females of childbearing potential are all other females who are menstruating, amenorrheic from previous medical treatments, under 50 years of age, and/or perimenopausal

- For all female patients:
  - Provide counseling not to share drug, not to donate blood, and on appropriate contraceptive use, including counseling on emergency contraception
  - Patients should be instructed to not extensively handle or open THALOMID® (thalidomide) Capsules and to maintain storage of capsules in blister packs until ingestion
  - Use the patient education materials provided in the *S.T.E.P.S.*® Patient Resource Pack

- For female patients of childbearing potential:
  - Female patients must thoroughly understand the need for two of the recommended forms of birth control beginning at least 4 weeks before therapy, during therapy, and for at least 4 weeks following discontinuation of THALOMID® (thalidomide) therapy
  - Contraceptive methods must include at least one highly effective method (e.g., intrauterine device [IUD], hormonal [birth control pills, injections, hormonal patches, or implants], tubal ligation, or partner's vasectomy) **AND** one additional effective barrier method (e.g., latex condom, diaphragm, or cervical cap)
  - If hormonal contraception is chosen as a highly effective method, concomitant use of prescription drugs including modafinil, penicillins, or certain herbal supplements such as St. John's Wort may reduce the effectiveness of the contraception and up to 1 month after discontinuation of these concomitant therapies. For patients using any hormonal therapy, one additional effective barrier method must be used AT THE SAME TIME
  - If hormonal or IUD contraception is medically contraindicated, another highly effective method or two barrier methods must be used **AT THE SAME TIME**
  - Perform an in-office pregnancy test, sensitive to at least 50 mIU/mL (urine or serum), even if continuous abstinence is the chosen method of birth control
    - The in-office pregnancy test must be performed, **with negative results**, within the 24 hours prior to beginning THALOMID® (thalidomide) therapy
  - Perform a pregnancy test weekly during the first 4 weeks of therapy
  - Pregnancy testing should be repeated every month if patient has regular menses or is amenorrheic, or every 2 weeks if irregular menses
  - Negative pregnancy tests are valid only for 7 days
  - Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding
  - If pregnancy does occur during treatment, THALOMID® (thalidomide) must be immediately discontinued. Any suspected fetal exposure to THALOMID® (thalidomide) must be reported immediately to the Celgene Customer Care Center at 1-888-423-5436. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling

Male Patients

- Provide counseling not to share drug, not to donate blood or sperm, and on contraceptive use, including counseling on emergency contraception
  - Patients should be instructed to not extensively handle or open THALOMID® (thalidomide) Capsules and to maintain storage of capsules in blister packs until ingestion
- Use the patient education materials provided in the *S.T.E.P.S.*® Patient Resource Pack
- Male patients must be instructed to always use a latex condom every time they have heterosexual sexual contact with a woman who is or can get pregnant, even if they have undergone a successful vasectomy, as THALOMID® (thalidomide) is present in semen. The risk to the fetus from the semen of male patients taking thalidomide is unknown

Completing Telephone Surveys

- Instruct the patient to complete a brief telephone survey by calling 1-888-423-5436
  - For all males, the Patient Registration/Patient-Physician Agreement Form is considered the initial telephone survey
- Prescriber will complete a brief telephone survey by calling 1-888-423-5436 for every patient before each prescription is written
  - An authorization number will be issued upon completion of the survey and must be written on the prescription. This prescription and authorization number is valid only for 7 days
  - Write authorization number on the prescription

Additional Prescribing Information

- Prescriptions cannot be issued by telephone; faxed prescriptions to pharmacies are permissible if state laws allow
- Prescribe no more than 4 weeks (28 days) of therapy, with no automatic refills
- Inform the patient that all prescriptions must be filled within 7 days

For Subsequent THALOMID® (thalidomide) Prescriptions

The prescriber must complete a brief telephone survey to obtain a new authorization number ***EVERY TIME*** a prescription for THALOMID® (thalidomide) is written.

For female patients:

- Repeat counseling for every patient
- Follow pregnancy test requirements as outlined in the Female Patients section
- Female patients must complete a brief telephone survey according to the following schedule:

  – Monthly
  - Adult females of childbearing potential
  - All female children

  – Every 6 months
  - Adult females not of childbearing potential

For male patients:

- Provide patient counseling as outlined in the Male Patients section
- Male patients must complete a brief telephone survey once a month

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

Patient Resource Pack

Printed in U.S.A. 02/07 THA05060R1

▼ Detach and affix to patient chart ▼

THALOMID®
(thalidomide) Capsules

Patient registration date: _____

Prescriber:

- Instruct the patient to complete a survey (check one):
  ❑ monthly ❑ every 6 months
- Complete prescriber survey with every prescription

Date of Visit	Date of Pregnancy Test (If applicable)	Prescriber Survey	Patient Survey*

*As described in Instructions for Prescribers.

1-888-423-5436
www.THALOMID.com

 Printed in U.S.A. 02/07 THA05061R1

System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
Patient Registration and Patient-Physician Agreement Form
Adult Male

WARNINGS:

1. 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 (REGARDLESS OF STRENGTH)] 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.

2. VENOUS THROMBOEMBOLIC EVENTS.

THE USE OF THALOMID® (thalidomide) IN MULTIPLE MYELOMA RESULTS IN AN INCREASED RISK OF VENOUS THROMBOEMBOLIC EVENTS, SUCH AS DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLUS. THIS RISK INCREASES SIGNIFICANTLY WHEN THALIDOMIDE IS USED IN COMBINATION WITH STANDARD CHEMOTHERAPEUTIC AGENTS INCLUDING DEXAMETHASONE. IN ONE CONTROLLED TRIAL, THE RATE OF VENOUS THROMBOEMBOLIC EVENTS WAS 22.5% IN PATIENTS RECEIVING THALIDOMIDE IN COMBINATION WITH DEXAMETHASONE COMPARED TO 4.9% IN PATIENTS RECEIVING DEXAMETHASONE ALONE (P=0.002). PATIENTS AND PHYSICIANS ARE ADVISED TO BE OBSERVANT FOR THE SIGNS AND SYMPTOMS OF THROMBOEMBOLISM. PATIENTS SHOULD BE INSTRUCTED TO SEEK MEDICAL CARE IF THEY DEVELOP SYMPTOMS SUCH AS SHORTNESS OF BREATH, CHEST PAIN, OR ARM OR LEG SWELLING. PRELIMINARY DATA SUGGEST THAT PATIENTS WHO ARE APPROPRIATE CANDIDATES MAY BENEFIT FROM CONCURRENT PROPHYLACTIC ANTICOAGULATION OR ASPIRIN TREATMENT.

AD1234567-7890

System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
Patient Registration and Patient-Physician Agreement Form
Adult Male

Patient/Authorized Representative: Please read thoroughly and initial inside of the box provided, if you agree with the statement:
Please keep a copy of this Patient-Physician Agreement Form for your records.

Initial

1. I understand that severe birth defects can occur with the use of THALOMID® (thalidomide). I have been warned by my doctor that any unborn baby will almost certainly have severe birth defects and can even die if a woman is pregnant or becomes pregnant while taking THALOMID® (thalidomide). ☐

2. I have been told by my doctor that I must NEVER have unprotected sexual contact with a woman who can become pregnant. Because THALOMID® (thalidomide) is present in semen, my doctor has explained that I must either completely abstain from sexual contact with women who are pregnant or able to become pregnant, or I must use a latex condom EVERY TIME I engage in any sexual contact with women who are pregnant or may become pregnant while taking THALOMID® (thalidomide) - and for 4 weeks after I stop taking the drug, even if I have had a successful vasectomy. ☐

3. I know that I must inform my doctor if I have had unprotected sexual contact with a woman who can become pregnant; or if I think, FOR ANY REASON, that my sexual partner may be pregnant. If my doctor is not available, I can call Celgene Drug Safety at 1-888-423-5436 or 1-888-668-2528 for information on emergency contraception. ☐

4. I understand that THALOMID® (thalidomide) will be prescribed ONLY for me. I must not share it with ANYONE, even someone who has similar symptoms to mine. It must be kept out of the reach of children and should NEVER be given to women who are able to have children. ☐

5. I agree any unused drug will be returned to Celgene by calling 1-888-423-5436. Shipping costs will be paid by Celgene. I understand that Celgene cannot provide patients with a refund for the unused drug. ☐

6. I have read the THALOMID® (thalidomide) patient brochure and/or viewed the videotape, "Important Information for Men and Women Taking THALOMID® (thalidomide)". I understand the contents, including other possible side effects from THALOMID® (thalidomide)". I know that I cannot donate blood or semen while taking THALOMID® (thalidomide). ☐

7. I understand that I must participate in a telephone survey and patient registry while I am on THALOMID® (thalidomide). ☐

8. My doctor has answered any questions I have asked. ☐

9. I understand that I might be asked to participate in an additional voluntary survey by mail or telephone to evaluate this *S.T.E.P.S.*® program. My agreement or disagreement will not interfere with my ability to receive THALOMID® (thalidomide). ☐

10. I acknowledge I may be contacted by a Celgene representative in regards to following the rules of the *S.T.E.P.S.*® program. ☐

AD1234567-7890

System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
Patient Registration and Patient-Physician Agreement Form
Adult Male

Authorization:
I understand that by signing this Authorization, I permit my healthcare providers and pharmacies to disclose to Celgene Corporation, its agents and contractors, my medical and other health information for the following purposes:

(a) coordinate the delivery of products and services available through pharmacies and Celgene's patient assistance programs;
(b) conduct data analyses regarding the use of THALOMID® (thalidomide);
(c) comply with applicable law;
(d) provide me with information regarding THALOMID® (thalidomide).

I understand that I may be contacted by Celgene or its agents and asked if I am willing to voluntarily answer additional survey questions that will help to evaluate *S.T.E.P.S.*®

This Authorization will be effective for 12 months after the date on which I stop receiving THALOMID® (thalidomide). However it may be revoked earlier, at any time, by me informing my healthcare provider that I will no longer participate in *S.T.E.P.S.*®

I understand that once my information is disclosed, there is no guarantee that the recipient of the information will not re-disclose it, and the recipient may not be required to abide by this Authorization.

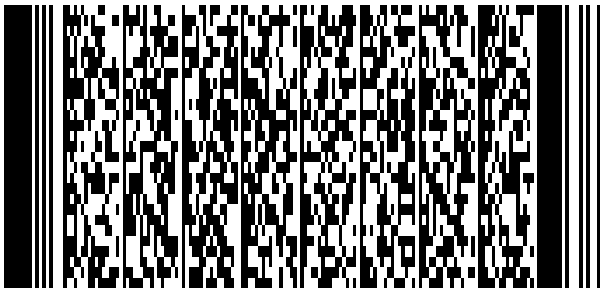
I understand that I may refuse to sign this Authorization. Such refusal constitutes a refusal to participate in *S.T.E.P.S.*® , and will affect my ability to receive THALOMID® (thalidomide).

I understand that I may refuse to participate in the voluntary survey. My refusal to participate in the survey will not change how my healthcare providers and pharmacies provide my medical treatment, and will not affect my ability to receive THALOMID® (thalidomide).

Yes_____ No_____ I authorize the information disclosure as described above.

Yes_____ No_____ I agree to participate in the voluntary survey described above.

UPON SIGNING THIS AUTHORIZATION, PATIENT HAS THE RIGHT TO OBTAIN A COPY, UPON REQUEST.



AD1234567-7890

System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
Patient Registration and Patient-Physician Agreement Form
Adult Male

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 also understand that the information I provide on this Patient-Physician Agreement Form and as part of ongoing surveys will be known by the manufacturer of THALOMID® (thalidomide) and the FDA. However, the information will not be used for commercial purposes.

The below party now authorizes my doctor to begin treatment with THALOMID® (thalidomide).

Date:	01-May-2007
Patient Name:	DOE, JOHN
Address:	1 MAIN ST, SUMMIT, NJ 07901
Telephone Number:	111-111-1111
Social Security No:	123-45-7890
Date of Birth:	01-Jan-1952
Sex:	M
ICD-9 Diagnosis Code:	203.0 MULTIPLE MYELOMA

Patient/Authorized Representative 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 has any questions regarding his 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:	DOE, MARK
DEA Number:	AD1234567
Social Security No:	--
Address:	11 MAIN STREET, SUMMIT, NJ 07901
Telephone Number:	111-111-1234
Fax Number:	111-111-1111

Prescriber Signature: _____

Date: _____

FAX THIS FORM TO 1-888-432-9325

AD1234567-7890

System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
Patient Registration and Patient-Physician Agreement Form
Male Child

WARNINGS:

1. 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 (REGARDLESS OF STRENGTH)] 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.

2. VENOUS THROMBOEMBOLIC EVENTS.

THE USE OF THALOMID® (thalidomide) IN MULTIPLE MYELOMA RESULTS IN AN INCREASED RISK OF VENOUS THROMBOEMBOLIC EVENTS, SUCH AS DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLUS. THIS RISK INCREASES SIGNIFICANTLY WHEN THALIDOMIDE IS USED IN COMBINATION WITH STANDARD CHEMOTHERAPEUTIC AGENTS INCLUDING DEXAMETHASONE. IN ONE CONTROLLED TRIAL, THE RATE OF VENOUS THROMBOEMBOLIC EVENTS WAS 22.5% IN PATIENTS RECEIVING THALIDOMIDE IN COMBINATION WITH DEXAMETHASONE COMPARED TO 4.9% IN PATIENTS RECEIVING DEXAMETHASONE ALONE (P=0.002). PATIENTS AND PHYSICIANS ARE ADVISED TO BE OBSERVANT FOR THE SIGNS AND SYMPTOMS OF THROMBOEMBOLISM. PATIENTS SHOULD BE INSTRUCTED TO SEEK MEDICAL CARE IF THEY DEVELOP SYMPTOMS SUCH AS SHORTNESS OF BREATH, CHEST PAIN, OR ARM OR LEG SWELLING. PRELIMINARY DATA SUGGEST THAT PATIENTS WHO ARE APPROPRIATE CANDIDATES MAY BENEFIT FROM CONCURRENT PROPHYLACTIC ANTICOAGULATION OR ASPIRIN TREATMENT.

AD1234567-7890

System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
Patient Registration and Patient-Physician Agreement Form
Male Child

Parent/Guardian: Please read thoroughly and initial inside of the box provided, if you agree with the statement:
Please keep a copy of this Patient-Physician Agreement Form for your records.

Initial

1. I understand that severe birth defects can occur with the use of THALOMID® (thalidomide). I have been warned by my child's doctor that any unborn baby will almost certainly have severe birth defects and can even die if a woman is pregnant or becomes pregnant while taking THALOMID® (thalidomide). ☐

2. I have been told by my child's doctor that the child in my care must NEVER have unprotected sexual contact with a woman who can become pregnant. Because THALOMID® (thalidomide) is present in semen, my child's doctor has explained that he must either completely abstain from sexual contact with women/girls who are pregnant or able to become pregnant or must use a latex condom EVERY TIME he engages in any sexual contact with women/girls who are pregnant or able to become pregnant while taking THALOMID® (thalidomide) - and for 4 weeks after he stops taking the drug. ☐

3. I also know that I must inform his doctor if he has unprotected sexual contact with a woman/girl who can become pregnant; or if I think, FOR ANY REASON, that his sexual partner may be pregnant. If his doctor is not available, I can call Celgene Drug Safety at 1-888-423-5436 or 1-888-668-2528 for information on emergency contraception. ☐

4. I understand that THALOMID® (thalidomide) will be prescribed ONLY for the child in my care. It must not be shared with ANYONE, even someone who has similar symptoms to the child in my care. It must be kept out of the reach of children and should NEVER be given to women/girls who are able to have children. ☐

5. I agree any unused drug will be returned to Celgene by calling 1-888-423-5436. Shipping costs will be paid by Celgene. I understand that Celgene cannot provide patients with a refund for the unused drug. ☐

6. I have read the THALOMID® (thalidomide) patient brochure and/or viewed the videotape, "Important Information for Men and Women Taking THALOMID® (thalidomide)". I understand the contents, including other possible side effects from THALOMID® (thalidomide). I know that he cannot donate blood or semen while taking THALOMID® (thalidomide). ☐

7. I understand that we must participate in a telephone survey and patient registry while the child in my care is taking THALOMID® (thalidomide). ☐

8. Our doctor has answered any questions that we have asked. ☐

9. I understand that we might be asked to participate in an additional voluntary survey by mail or telephone to evaluate the *S.T.E.P.S.*® program. Our agreement or disagreement will not interfere with my child's ability to receive THALOMID® (thalidomide). ☐

10. I acknowledge that we may be contacted by a Celgene representative in regards to the *S.T.E.P.S.*® program. ☐

AD1234567-7890

System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
Patient Registration and Patient-Physician Agreement Form
Male Child

Authorization:
I understand that by signing this Authorization, I permit my healthcare providers and pharmacies to disclose to Celgene Corporation, its agents and contractors, my medical and other health information for the following purposes:

(a) coordinate the delivery of products and services available through pharmacies and Celgene's patient assistance programs;
(b) conduct data analyses regarding the use of THALOMID® (thalidomide);
(c) comply with applicable law;
(d) provide me with information regarding THALOMID® (thalidomide).

I understand that I may be contacted by Celgene or its agents and asked if I am willing to voluntarily answer additional survey questions that will help to evaluate *S.T.E.P.S.*®

This Authorization will be effective for 12 months after the date on which I stop receiving THALOMID® (thalidomide). However it may be revoked earlier, at any time, by me informing my healthcare provider that I will no longer participate in *S.T.E.P.S.*®

I understand that once my information is disclosed, there is no guarantee that the recipient of the information will not re-disclose it, and the recipient may not be required to abide by this Authorization.

I understand that I may refuse to sign this Authorization. Such refusal constitutes a refusal to participate in *S.T.E.P.S.*® , and will affect my ability to receive THALOMID® (thalidomide).

I understand that I may refuse to participate in the voluntary survey. My refusal to participate in the survey will not change how my healthcare providers and pharmacies provide my medical treatment, and will not affect my ability to receive THALOMID® (thalidomide).

Yes_____ No_____ I authorize the information disclosure as described above.

Yes_____ No_____ I agree to participate in the voluntary survey described above.

UPON SIGNING THIS AUTHORIZATION, PATIENT HAS THE RIGHT TO OBTAIN A COPY, UPON REQUEST.

AD1234567-7890

System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
Patient Registration and Patient-Physician Agreement Form
Male Child

This information has been read aloud to us in the language of our choice. I understand that if we do not follow all of our doctor's instructions, the child in my care will not be able to receive THALOMID® (thalidomide). I also understand that the information we provide on this Patient-Physician Agreement Form and as part of ongoing surveys will be known by the manufacturer of THALOMID® (thalidomide) and the FDA. However, the information will not be used for commercial purposes.

The below party now authorizes my child's doctor to begin treating the child in my care with THALOMID® (thalidomide).

Date:	01-May-2007
Patient Name:	DOE, JOHN
Address:	1 MAIN ST, SUMMIT, NJ 07901
Telephone Number:	111-111-1111
Social Security No:	123-45-7890
Date of Birth:	01-Jan-1999
Sex:	M
ICD-9 Diagnosis Code:	203.0 MULTIPLE MYELOMA

Parent/Guardian Signature: _____

Date: _____

I have fully explained to the parent/guardian the nature, purpose, and risks of the treatment described above, especially the risks to women of childbearing potential. I have asked the parent/guardian if he/she has any questions regarding the child's 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:	DOE, MARK
DEA Number:	AD1234567
Social Security No:	--
Address:	11 MAIN STREET, SUMMIT, NJ 07901
Telephone Number:	111-111-1234
Fax Number:	111-111-1111

Prescriber Signature: _____

Date: _____

FAX THIS FORM TO 1-888-432-9325

AD1234567-7890

System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
Patient Registration and Patient-Physician Agreement Form
Adult Female Not of Childbearing Potential

WARNINGS:

1. 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 (REGARDLESS OF STRENGTH)] 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.

2. VENOUS THROMBOEMBOLIC EVENTS.

THE USE OF THALOMID® (thalidomide) IN MULTIPLE MYELOMA RESULTS IN AN INCREASED RISK OF VENOUS THROMBOEMBOLIC EVENTS, SUCH AS DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLUS. THIS RISK INCREASES SIGNIFICANTLY WHEN THALIDOMIDE IS USED IN COMBINATION WITH STANDARD CHEMOTHERAPEUTIC AGENTS INCLUDING DEXAMETHASONE. IN ONE CONTROLLED TRIAL, THE RATE OF VENOUS THROMBOEMBOLIC EVENTS WAS 22.5% IN PATIENTS RECEIVING THALIDOMIDE IN COMBINATION WITH DEXAMETHASONE COMPARED TO 4.9% IN PATIENTS RECEIVING DEXAMETHASONE ALONE (P=0.002). PATIENTS AND PHYSICIANS ARE ADVISED TO BE OBSERVANT FOR THE SIGNS AND SYMPTOMS OF THROMBOEMBOLISM. PATIENTS SHOULD BE INSTRUCTED TO SEEK MEDICAL CARE IF THEY DEVELOP SYMPTOMS SUCH AS SHORTNESS OF BREATH, CHEST PAIN, OR ARM OR LEG SWELLING. PRELIMINARY DATA SUGGEST THAT PATIENTS WHO ARE APPROPRIATE CANDIDATES MAY BENEFIT FROM CONCURRENT PROPHYLACTIC ANTICOAGULATION OR ASPIRIN TREATMENT.

AD1234567-7890

System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
Patient Registration and Patient-Physician Agreement Form
Adult Female Not of Childbearing Potential

Patient/Authorized Representative: Please read thoroughly and initial inside of the box provided if you agree with the statement:
Please keep a copy of this Patient-Physician Agreement Form for your records.

	Initial
1. I understand that severe birth defects can occur with the use of THALOMID® (thalidomide). I have been warned by my doctor that any unborn baby will almost certainly have severe birth defects and can even die if a woman is pregnant or becomes pregnant while taking THALOMID® (thalidomide).	☐
2. I certify that I am not now pregnant, nor am I of childbearing potential as I have been in a natural menopause for at least 24 months (been through the changes of life); or I had my uterus/womb completely removed (hysterectomy).	☐
3. I understand that THALOMID® (thalidomide) will be prescribed ONLY for me. I must not share it with ANYONE, even someone who has similar symptoms to mine. It must be kept out of the reach of children and should NEVER be given to women who are able to have children.	☐
4. I agree any unused drug will be returned to Celgene by calling 1-888-423-5436. Shipping costs will be paid by Celgene. I understand that Celgene cannot provide patients with a refund for the unused drug.	☐
5. I have read the THALOMID® (thalidomide) patient brochure and/or viewed the videotape, "Important Information for Men and Women Taking THALOMID® (thalidomide)". I understand the contents, including other possible side effects from THALOMID® (thalidomide). I know that I cannot donate blood while taking THALOMID® (thalidomide).	☐
6. I understand that I must participate in a telephone survey and patient registry while I am on THALOMID® (thalidomide).	☐
7. My doctor has answered any questions I have asked.	☐
8. I understand that I might be asked to participate in an additional voluntary survey by mail or telephone to evaluate this *S.T.E.P.S.*® program. My agreement or disagreement will not interfere with my ability to receive THALOMID® (thalidomide).	☐
9. I acknowledge I may be contacted by a Celgene representative in regards to following the rules with the *S.T.E.P.S.*® program.	☐

AD1234567-7890

System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
Patient Registration and Patient-Physician Agreement Form
Adult Female Not of Childbearing Potential

Authorization:
I understand that by signing this Authorization, I permit my healthcare providers and pharmacies to disclose to Celgene Corporation, its agents and contractors, my medical and other health information for the following purposes:

(a) coordinate the delivery of products and services available through pharmacies and Celgene's patient assistance programs;
(b) conduct data analyses regarding the use of THALOMID® (thalidomide);
(c) comply with applicable law;
(d) provide me with information regarding THALOMID® (thalidomide).

I understand that I may be contacted by Celgene or its agents and asked if I am willing to voluntarily answer additional survey questions that will help to evaluate *S.T.E.P.S.*®

This Authorization will be effective for 12 months after the date on which I stop receiving THALOMID® (thalidomide). However it may be revoked earlier, at any time, by me informing my healthcare provider that I will no longer participate in *S.T.E.P.S.*®

I understand that once my information is disclosed, there is no guarantee that the recipient of the information will not re-disclose it, and the recipient may not be required to abide by this Authorization.

I understand that I may refuse to sign this Authorization. Such refusal constitutes a refusal to participate in *S.T.E.P.S.*® , and will affect my ability to receive THALOMID® (thalidomide).

I understand that I may refuse to participate in the voluntary survey. My refusal to participate in the survey will not change how my healthcare providers and pharmacies provide my medical treatment, and will not affect my ability to receive THALOMID® (thalidomide).

Yes_____ No_____ I authorize the information disclosure as described above.

Yes_____ No_____ I agree to participate in the voluntary survey described above.

UPON SIGNING THIS AUTHORIZATION, PATIENT HAS THE RIGHT TO OBTAIN A COPY, UPON REQUEST.

AD1234567-7890

System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
Patient Registration and Patient-Physician Agreement Form
Adult Female Not of Childbearing Potential

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 also understand that the information I provide on this Patient-Physician Agreement Form and as part of ongoing surveys will be known by the manufacturer of THALOMID® (thalidomide) and the FDA. However, the information will not be used for commercial purposes.

The below party now authorizes her doctor to begin treatment with THALOMID® (thalidomide).

Date:	01-May-2007	No	No	Yes

Patient Name: DOE, JANE
Address: 1 MAIN ST, SUMMIT, NJ 07901
Telephone Number: 111-111-1111
Social Security No: 123-45-7890
Date of Birth: 01-Jan-1952
Sex: F
ICD-9 Diagnosis Code: 203.0 MULTIPLE MYELOMA

Patient/Authorized Representative 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 she has any questions regarding 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: DOE, MARK
DEA Number: AD1234567
Social Security No: --
Address: 11 MAIN STREET, SUMMIT, NJ 07901
Telephone Number: 111-111-1234
Fax Number: 111-111-1111

Prescriber Signature: _____

Date: _____

FAX THIS FORM TO 1-888-432-9325

AD1234567-7890

System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
Patient Registration and Patient-Physician Agreement Form
Adult Female of Childbearing Potential

WARNINGS:

1. SEVERE, LIFE-THREATENING HUMAN BIRTH DEFECTS.

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AD1234567-7890

System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
Patient Registration and Patient-Physician Agreement Form
Adult Female of Childbearing Potential

Patient/Authorized Representative: Please read thoroughly and initial inside of the box provided, if you agree with the statement:
Please keep a copy of this Patient-Physician Agreement Form for your records.

Initial

1. I understand that severe birth defects can occur with the use of THALOMID® (thalidomide). I have been warned by my doctor that my unborn baby will almost certainly have severe birth defects and can even die if I am pregnant or become pregnant while taking THALOMID® (thalidomide). ☐

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

3. If I am having sexual relations with a man, and I am less than 50 years of age, and/or menses stopped due to treatment of my disease, I understand I am able to become pregnant. I must use at least one highly effective method and one additional effective method of birth control (contraception) AT THE SAME TIME: ☐

At least one highly effective method	**AND**	**One additional effective method**
IUD		Latex condom
Hormonal (birth control pills, injections, patch, implants)		Diaphragm
Tubal ligation (tubes tied)		Cervical cap
Partner's vasectomy		

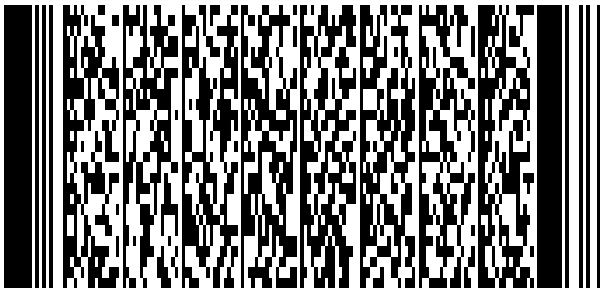
These birth control methods must be used for at least 4 weeks before starting THALOMID® (thalidomide) therapy, all during THALOMID® (thalidomide) therapy, and for at least 4 weeks after THALOMID® (thalidomide) therapy has stopped. I must use these methods unless I completely abstain from heterosexual sexual contact. If a hormonal (birth control pills, injections, patch, or implants) or IUD method is not medically possible for me, I may use another highly effective method or two barrier methods AT THE SAME TIME.

4. I know that I must have a pregnancy test done by my doctor within 24 hours prior to starting THALOMID® (thalidomide) therapy, even if I have not had my menses due to treatment of my disease, then every week during the first 4 weeks of THALOMID® (thalidomide) therapy. I will then have a pregnancy test every 4 weeks if I have regular and/or no menstrual cycles, or every 2 weeks if my cycles are irregular while I am taking THALOMID® (thalidomide). ☐

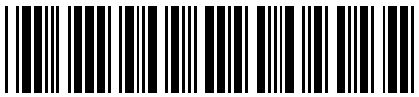
5. I know that I must immediately stop taking THALOMID® (thalidomide) and inform my doctor if I become pregnant while taking the drug; if I miss my menstrual period, or experience unusual menstrual bleeding; stop using birth control; or think, FOR ANY REASON, that I may be pregnant. If my doctor is not available, I can call Celgene Drug Safety at 1-888-423-5436 or 1-888-668-2528 for information on emergency contraception. ☐

6. I am not now pregnant, nor will I try to become pregnant for at least 4 weeks after I have completely finished taking THALOMID® (thalidomide). ☐

7. I understand that THALOMID® (thalidomide) will be prescribed ONLY for me. I must NOT share it with ANYONE, even someone who has similar symptoms to mine. It must be kept out of the reach of children and should NEVER be given to women who are able to have children. ☐



AD1234567-7890



System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
Patient Registration and Patient-Physician Agreement Form
Adult Female of Childbearing Potential

8. I agree any unused drug will be returned to Celgene by calling 1-888-423-5436. Shipping costs will be paid by Celgene. I understand that Celgene cannot provide patients with a refund for the unused drug. ☐

9. I have read the THALOMID® (thalidomide) patient brochure and/or viewed the videotape, "Important Information for Men and Women Taking THALOMID® (thalidomide)". I understand the contents, including other possible side effects from THALOMID® (thalidomide). I know that I cannot donate blood while taking THALOMID® (thalidomide). ☐

10. I understand that I must participate in a telephone survey and patient registry while I am on THALOMID® (thalidomide). ☐

11. My doctor has answered any questions I have asked. ☐

12. I understand that I might be asked to participate in an additional voluntary survey by mail or telephone to evaluate the *S.T.E.P.S.*® program. My agreement or disagreement will not interfere with my ability to receive THALOMID® (thalidomide). ☐

13.I acknowledge I may be contacted by a Celgene representative in regards to following the rules with the *S.T.E.P.S.*® program. ☐

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System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
Patient Registration and Patient-Physician Agreement Form
Adult Female of Childbearing Potential

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(a) coordinate the delivery of products and services available through pharmacies and Celgene's patient assistance programs;
(b) conduct data analyses regarding the use of THALOMID® (thalidomide);
(c) comply with applicable law;
(d) provide me with information regarding THALOMID® (thalidomide).

I understand that I may be contacted by Celgene or its agents and asked if I am willing to voluntarily answer additional survey questions that will help to evaluate *S.T.E.P.S.*®

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I understand that I may refuse to participate in the voluntary survey. My refusal to participate in the survey will not change how my healthcare providers and pharmacies provide my medical treatment, and will not affect my ability to receive THALOMID® (thalidomide).

Yes_____ No_____ I authorize the information disclosure as described above.

Yes_____ No_____ I agree to participate in the voluntary survey described above.

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AD1234567-7890

System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
Patient Registration and Patient-Physician Agreement Form
Adult Female of Childbearing Potential

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 also understand that the information I provide on this Patient-Physician Agreement Form and as part of ongoing surveys will be known by the manufacturer of THALOMID® (thalidomide) and the FDA. However, the information will not be used for commercial purposes.

The below party now authorizes my doctor to begin treatment with THALOMID® (thalidomide).

Date:	01-May-2007	Yes	No	No

Patient Name: DOE, JANE
Address: 1 MAIN ST, SUMMIT, NJ 07901
Telephone Number: 111-111-1111
Social Security No: 123-45-7890
Date of Birth: 01-Jan-1972
Sex: F
ICD-9 Diagnosis Code: 203.0 MULTIPLE MYELOMA

Patient/Authorized Representative 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 she has any questions regarding 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: DOE, MARK
DEA Number: AD1234567
Social Security No: --
Address: 11 MAIN STREET, SUMMIT, NJ 07901
Telephone Number: 111-111-1234
Fax Number: 111-111-1111

Prescriber Signature: _____

Date: _____

FAX THIS FORM TO 1-888-432-9325

AD1234567-7890

System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
Patient Registration and Patient-Physician Agreement Form
Female Child Not of Childbearing Potential

WARNINGS:

1. 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 (REGARDLESS OF STRENGTH)] 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.

2. VENOUS THROMBOEMBOLIC EVENTS.

THE USE OF THALOMID® (thalidomide) IN MULTIPLE MYELOMA RESULTS IN AN INCREASED RISK OF VENOUS THROMBOEMBOLIC EVENTS, SUCH AS DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLUS. THIS RISK INCREASES SIGNIFICANTLY WHEN THALIDOMIDE IS USED IN COMBINATION WITH STANDARD CHEMOTHERAPEUTIC AGENTS INCLUDING DEXAMETHASONE. IN ONE CONTROLLED TRIAL, THE RATE OF VENOUS THROMBOEMBOLIC EVENTS WAS 22.5% IN PATIENTS RECEIVING THALIDOMIDE IN COMBINATION WITH DEXAMETHASONE COMPARED TO 4.9% IN PATIENTS RECEIVING DEXAMETHASONE ALONE (P=0.002). PATIENTS AND PHYSICIANS ARE ADVISED TO BE OBSERVANT FOR THE SIGNS AND SYMPTOMS OF THROMBOEMBOLISM. PATIENTS SHOULD BE INSTRUCTED TO SEEK MEDICAL CARE IF THEY DEVELOP SYMPTOMS SUCH AS SHORTNESS OF BREATH, CHEST PAIN, OR ARM OR LEG SWELLING. PRELIMINARY DATA SUGGEST THAT PATIENTS WHO ARE APPROPRIATE CANDIDATES MAY BENEFIT FROM CONCURRENT PROPHYLACTIC ANTICOAGULATION OR ASPIRIN TREATMENT.

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System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
Patient Registration and Patient-Physician Agreement Form
Female Child Not of Childbearing Potential

Patient/Guardian: Please read thoroughly and initial inside of the box provided, if you agree with the statement:
Please keep a copy of this Patient-Physician Agreement Form for your records.

	Initial
1. I understand that severe birth defects can occur with the use of THALOMID® (thalidomide). I have been warned by my child's doctor that any unborn baby will almost certainly have severe birth defects and can even die if a woman is pregnant or becomes pregnant while taking THALOMID® (thalidomide).	☐
2. I certify that the child in my care is not now pregnant, nor is she 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.	☐
3. I understand that THALOMID® (thalidomide) will be prescribed ONLY for the child in my care. It must not be shared with ANYONE, even someone who has similar symptoms to the child in my care. It must be kept out of the reach of children and should NEVER be given to women/girls who are able to have children.	☐
4. I agree any unused drug will be returned to Celgene by calling 1-888-423-5436. Shipping costs will be paid by Celgene. I understand that Celgene cannot provide patients with a refund for the unused drug.	☐
5. I have read the THALOMID® (thalidomide) patient brochure and/or viewed the videotape, "Important Information for Men and Women Taking THALOMID® (thalidomide)". I understand the contents, including other possible side effects from THALOMID® (thalidomide). I know that she cannot donate blood while taking THALOMID® (thalidomide).	☐
6. I understand that we must participate in a telephone survey and patient registry while the child in my care is on THALOMID® (thalidomide).	☐
7. Our doctor has answered any questions that we have asked.	☐
8. I understand that we might be asked to participate in an additional voluntary survey by mail or telephone to evaluate the *S.T.E.P.S.*® program. Our agreement or disagreement will not interfere with my child's ability to receive THALOMID® (thalidomide).	☐
9. I acknowledge that we may be contacted by a Celgene representative in regards to my child following the rules with the *S.T.E.P.S.*® program.	☐

AD1234567-7890

System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
Patient Registration and Patient-Physician Agreement Form
Female Child Not of Childbearing Potential

Authorization:
I understand that by signing this Authorization, I permit my healthcare providers and pharmacies to disclose to Celgene Corporation, its agents and contractors, my medical and other health information for the following purposes:

(a) coordinate the delivery of products and services available through pharmacies and Celgene's patient assistance programs;
(b) conduct data analyses regarding the use of THALOMID® (thalidomide);
(c) comply with applicable law;
(d) provide me with information regarding THALOMID® (thalidomide).

I understand that I may be contacted by Celgene or its agents and asked if I am willing to voluntarily answer additional survey questions that will help to evaluate *S.T.E.P.S.*®

This Authorization will be effective for 12 months after the date on which I stop receiving THALOMID® (thalidomide). However it may be revoked earlier, at any time, by me informing my healthcare provider that I will no longer participate in *S.T.E.P.S.*®

I understand that once my information is disclosed, there is no guarantee that the recipient of the information will not re-disclose it, and the recipient may not be required to abide by this Authorization.

I understand that I may refuse to sign this Authorization. Such refusal constitutes a refusal to participate in *S.T.E.P.S.*® , and will affect my ability to receive THALOMID® (thalidomide).

I understand that I may refuse to participate in the voluntary survey. My refusal to participate in the survey will not change how my healthcare providers and pharmacies provide my medical treatment, and will not affect my ability to receive THALOMID® (thalidomide).

Yes_____ No_____ I authorize the information disclosure as described above.

Yes_____ No_____ I agree to participate in the voluntary survey described above.

UPON SIGNING THIS AUTHORIZATION, PATIENT HAS THE RIGHT TO OBTAIN A COPY, UPON REQUEST.

AD1234567-7890

System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
Patient Registration and Patient-Physician Agreement Form
Female Child Not of Childbearing Potential

This information has been read aloud to us in the language of our choice. I understand that if we do not follow all of our doctor's instructions, the child in my care will not be able to receive THALOMID® (thalidomide). I also understand that the information we provide on this Patient-Physician Agreement Form and as part of ongoing surveys will be known by the manufacturer of THALOMID® (thalidomide) and the FDA. However, the information will not be used for commercial purposes.

The below party now authorizes my child's doctor to begin treating the child in my care with THALOMID® (thalidomide).

Date:	01-May-2007	No		

Patient Name: DOE, JANE
Address: 1 MAIN ST, SUMMIT, NJ 07901
Telephone Number: 111-111-1111
Social Security No: 123-45-7890
Date of Birth: 01-Jan-1999
Sex: F
ICD-9 Diagnosis Code: 203.0 MULTIPLE MYELOMA

Parent/Guardian Signature: _____

Date: _____

I have fully explained to the parent/guardian the nature, purpose, and risks of the treatment described above, especially the risks to women of childbearing potential. I have asked the parent/guardian if he/she has any questions regarding the child's 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: DOE, MARK
DEA Number: AD1234567
Social Security No: --
Address: 11 MAIN STREET, SUMMIT, NJ 07901
Telephone Number: 111-111-1234
Fax Number: 111-111-1111

Prescriber Signature: _____

Date: _____

FAX THIS FORM TO 1-888-432-9325

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Patient Registration and Patient-Physician Agreement Form
Female Child of Childbearing Potential

Patient/Guardian: Please read thoroughly and initial inside of the box provided, if you agree with the statement:
Please keep a copy of this Patient-Physician Agreement Form for your records.

Initial

1. I understand that the child in my care 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. ☐

2. I understand that severe birth defects can occur with the use of THALOMID® (thalidomide). I have been warned by our doctor that an unborn baby will almost certainly have severe birth defects or may even die if the child in my care is pregnant or becomes pregnant while taking THALOMID® (thalidomide). ☐

3. I understand that if the child in my care 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, patch, implants)		Diaphragm
Tubal ligation (tubes tied)		Cervical cap
Partner's vasectomy		

These birth control methods must be used for at least 4 weeks before starting THALOMID® (thalidomide) therapy, all during THALOMID® (thalidomide) therapy, and for at least 4 weeks after THALOMID® (thalidomide) therapy has stopped. She must use these methods unless she completely abstains from heterosexual sexual contact. If a hormonal (birth control pills, injections, patch, or implants) or IUD method is not medically possible for her, she may use another highly effective method or two barrier methods AT THE SAME TIME.

4. I know that the child in my care must have a pregnancy test done by our doctor within the 24 hours prior to starting THALOMID® (thalidomide) therapy, even if my child's menses has stopped due to treatment for my child's disease. Then every week during the first 4 weeks of THALOMID® (thalidomide) therapy. She will then have a pregnancy test every 4 weeks if she has regular and/or no menstrual cycles, or every 2 weeks if her cycles are irregular while she is taking THALOMID® (thalidomide). ☐

5. I know that the child in my care must immediately stop taking THALOMID® (thalidomide) and that I must inform our doctor if she becomes pregnant while taking the drug; if she misses her menstrual period, or experiences unusual menstrual bleeding; stops using birth control; or thinks, FOR ANY REASON, that she may be pregnant. If our doctor is not available, I can call Celgene Drug Safety at 1-888-423-5436 or 1-888-668-2528 for emergency contraception. ☐

6. The child in my care is not now pregnant, nor will she try to become pregnant for at least 4 weeks after she has completely finished taking THALOMID® (thalidomide). ☐

System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®)
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7. I understand that THALOMID® (thalidomide) will be prescribed ONLY for the child in my care. She must not share it with ANYONE, even someone who has similar symptoms to her. It must be kept out of the reach of children and should NEVER be given to women who are able to have children. ☐

8. I agree any unused drug will be returned to Celgene by calling 1-888-423-5436. Shipping costs will be paid by Celgene. I understand that Celgene cannot provide patients with a refund for the unused drug. ☐

9. I have read the THALOMID® (thalidomide) patient brochure and/or viewed the videotape, "Important Information for Men and Women Taking THALOMID® (thalidomide)". I understand the contents, including other possible side effects from THALOMID® (thalidomide). I know that she cannot donate blood while taking THALOMID® (thalidomide). ☐

10. I understand that we must participate in a telephone survey and patient registry while she is on THALOMID® (thalidomide). ☐

11. Our doctor has answered any questions that we have asked. ☐

12. I understand that we might be asked to participate in an additional voluntary survey by mail or telephone to evaluate the *S.T.E.P.S.*® program. Our agreement or disagreement will not interfere with my child's ability to receive THALOMID® (thalidomide). ☐

13. I acknowledge that we may be contacted by a Celgene representative in regards to my child following the rules with the *S.T.E.P.S.*® program. ☐

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(a) coordinate the delivery of products and services available through pharmacies and Celgene's patient assistance programs;
(b) conduct data analyses regarding the use of THALOMID® (thalidomide);
(c) comply with applicable law;
(d) provide me with information regarding THALOMID® (thalidomide).

I understand that I may be contacted by Celgene or its agents and asked if I am willing to voluntarily answer additional survey questions that will help to evaluate *S.T.E.P.S.*®

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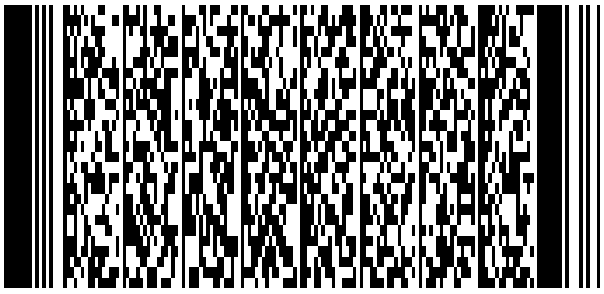
I understand that I may refuse to sign this Authorization. Such refusal constitutes a refusal to participate in *S.T.E.P.S.*® , and will affect my ability to receive THALOMID® (thalidomide).

I understand that I may refuse to participate in the voluntary survey. My refusal to participate in the survey will not change how my healthcare providers and pharmacies provide my medical treatment, and will not affect my ability to receive THALOMID® (thalidomide).

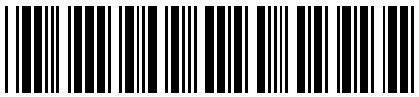
Yes_____ No_____ I authorize the information disclosure as described above.

Yes_____ No_____ I agree to participate in the voluntary survey described above.

UPON SIGNING THIS AUTHORIZATION, PATIENT HAS THE RIGHT TO OBTAIN A COPY, UPON REQUEST.



AD1234567-7890



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Female Child of Childbearing Potential

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The below party now authorizes my child's doctor to begin treating the child in my care with THALOMID® (thalidomide).

Date:	01-May-2007	Yes		

Patient Name: DOE, JANE
Address: 1 MAIN ST, SUMMIT, NJ 07901
Telephone Number: 111-111-1111
Social Security No: 123-45-7890
Date of Birth: 01-Jan-1990
Sex: F
ICD-9 Diagnosis Code: 203.0 MULTIPLE MYELOMA

Parent/Guardian Signature: _____

Date: _____

I have fully explained to the parent/guardian the nature, purpose, and risks of the treatment described above, especially the risks to women of childbearing potential. I have asked the parent/guardian if he/she has any questions regarding the child's 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: DOE, MARK
DEA Number: AD1234567
Social Security No: --
Address: 11 MAIN STREET, SUMMIT, NJ 07901
Telephone Number: 111-111-1234
Fax Number: 111-111-1111

Prescriber Signature: _____

Date: _____

FAX THIS FORM TO 1-888-432-9325

AD1234567-7890

Pharmacy Registration

All pharmacies MUST be registered to dispense THALOMID® (thalidomide). The following procedure MUST be completed with every dispense. This signed registration card MUST be returned to Celgene Corporation.

Before dispensing THALOMID® (thalidomide), I agree to:

- Only accept prescriptions with an authorization number. All prescriptions and authorization numbers are valid for 7 days (telephone prescriptions are not permitted). Faxed prescriptions may be permissible depending on state laws
- Call in the authorization number on every prescription to Celgene at 1-888-423-5436 and obtain a confirmation number to dispense THALOMID® (thalidomide)
- Write the confirmation number on the prescription
- Dispense no more than a 4-week (28-day) supply, with no automatic refills
- DISPENSE SUBSEQUENT PRESCRIPTIONS ONLY IF FEWER THAN 7 DAYS OF THERAPY REMAIN ON THE PREVIOUS PRESCRIPTION
- Dispense blister packs intact; capsules cannot be repackaged
- Not redistribute or transfer THALOMID® (thalidomide) between pharmacies
- Have all staff pharmacists educated about the dispensing procedure for THALOMID® (thalidomide) by the head pharmacist or director of pharmacy

Registration must be signed by the head pharmacist or director of pharmacy.

Please fill out the spaces below completely.

Pharmacy Name _____ Store Number _____

Pharmacist Name _____ Title _____

NABP (or DEA) No. _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Pharmacy Hours _____

Email Address _____

Designee for *S.T.E.P.S.*®-Related Questions _____

I understand that if I fail to comply with <u>all</u> requirements of the *S.T.E.P.S.*® program, my pharmacy may not be permitted to purchase/dispense THALOMID® (thalidomide). *S.T.E.P.S.*® is an FDA-mandated program.

Signature _____ Date _____

Return this card to the Celgene Customer Care Center via mail or by fax (1-888-432-9325).

THALOMID®
(thalidomide) Capsules

Celgene

Printed in U.S.A. 02/07 THA05069R1

Fold, peel strip, and seal.

NO POSTAGE
NECESSARY
IF MAILED
IN THE
UNITED STATES

BUSINESS REPLY MAIL
FIRST-CLASS MAIL PERMIT NO. 101 SUMMIT NJ

POSTAGE WILL BE PAID BY ADDRESSEE

CELGENE CORPORATION
CELGENE CUSTOMER CARE CENTER
86 MORRIS AVENUE
SUMMIT NJ 07901-9920

Guidelines for Dispensing/Ordering THALOMID® (thalidomide) Capsules

Dear Pharmacist:

- Place orders for THALOMID® (thalidomide) capsules through your wholesaler; once shipment is received, usually in 1–2 days, follow the process below
- In the event that you do not receive your THALOMID® (thalidomide) order, contact your wholesaler
- Only accept prescriptions with an authorization number. Prescriptions and authorization numbers are valid only for 7 days (telephone prescriptions are not permitted)
- Faxed prescriptions are permissible depending on state laws
- Call each unique authorization number on every prescription into the automated system at the **Celgene Customer Care Center,** open 24 hours a day, 7 days a week, at **1-888-423-5436**
  - Enter NABP # or DEA #
  - Enter authorization number written on prescription
  - Enter number of capsules and milligram (mg) strength being dispensed
- Write the confirmation number on the prescription
- Dispense no more than a 4-week (28-day) supply. A new prescription is required for further dispensing
- **DISPENSE SUBSEQUENT PRESCRIPTIONS ONLY IF FEWER THAN 7 DAYS OF THERAPY REMAIN ON THE PREVIOUS PRESCRIPTION**
- Dispense blister packs intact; capsules cannot be repackaged. In the event the amount of total capsules written on the prescription is not divisible by 28, contact the prescriber regarding packaging guidelines
- THALOMID® (thalidomide) inventory cannot be transferred to another pharmacy
- Educate all staff pharmacists about the dispensing procedure for THALOMID® (thalidomide)

If you have any questions, please call the **Celgene Customer Care Center** at **1-888-423-5436.**

Please see full Prescribing Information, including Boxed WARNINGS, CONTRAINDICATIONS, PRECAUTIONS, and ADVERSE REACTIONS, enclosed in pocket.

THALOMID® (thalidomide) Capsules

Celgene®

Celgene Customer Care Center 1-888-423-5436 • Fax (1-888-432-9325) • www.THALOMID.com
86 Morris Avenue, Summit, NJ 07901

Multiple Myeloma

THALOMID® (thalidomide) in combination with dexamethasone is indicated for the treatment of patients with newly diagnosed multiple myeloma.

The effectiveness of THALOMID® is based on response rates (**see CLINICAL STUDIES section**). There are no controlled trials demonstrating a clinical benefit, such as an improvement in survival.

Erythema Nodosum Leprosum

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.

WARNINGS:

1. SEVERE, LIFE-THREATENING HUMAN BIRTH DEFECTS.

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IMPORTANT SAFETY INFORMATION

Hypersensitivity: THALOMID® (thalidomide) is contraindicated in any patients who have demonstrated hypersensitivity to the drug or its components.

Nursing mothers: It is not known whether THALOMID® (thalidomide) is excreted in human milk. Because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Peripheral neuropathy: THALOMID® (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.

Other most common adverse events: Multiple Myeloma (THALOMID®/dexamethasone): The most frequently reported adverse events were constipation (55%), sensory neuropathy (54%), confusion (28%), hypocalcemia (72%), edema (57%), dyspnea (42%), thrombosis/embolism (23%), and rash/desquamation (30%) (occurring in ≥20% of patients and with a frequency ≥10% in patients treated with THALOMID®/dexamethasone compared with dexamethasone alone).

ENL (THALOMID®): The most frequently reported adverse events were somnolence (38%), rash (21%), headache (13%), asthenia (8%), impotence (8%), malaise (8%), pain (8%), pruritus (8%), and vertigo (8%) (occurring in ≥5% of patients). In placebo-controlled clinical trials of HIV-seropositive patient populations, there have been reports of increased plasma HIV RNA levels.

THALOMID must be administered in compliance with all of the terms outlined in the *S.T.E.P.S.*® program by prescribers, pharmacists, and patients registered with *S.T.E.P.S.*®. Patients should be instructed to not extensively handle or open thalidomide capsules and to maintain storage of capsules in blister packs until ingestion.

Please see full Prescribing Information, including Boxed WARNINGS, CONTRAINDICATIONS, PRECAUTIONS, and ADVERSE REACTIONS, enclosed in pocket.

For further information about THALOMID®, please call the Celgene Customer Care Center at 1-888-423-5436 or visit www.THALOMID.com

Printed in U.S.A. 09/06 THA05074R1

Prescriber Registration

All prescribers MUST be registered to prescribe THALOMID® (thalidomide). Please review the steps below that MUST be followed with every patient and return this card to Celgene Corporation.

When prescribing THALOMID® (thalidomide), I agree to:

- Provide patient counseling on the benefits and risks of THALOMID® (thalidomide) therapy
- Provide contraception and emergency contraception counseling in addition to scheduled pregnancy testing
- Submit a completed Patient Registration/Patient-Physician Agreement Form for each new patient to the Celgene Customer Care Center via fax to 1-888-432-9325
- Complete a brief prescriber telephone survey for every patient and obtain a new authorization number for each prescription written
- Write the authorization number on every prescription
- Facilitate compliance with a mandatory patient monitoring telephone survey
- Prescribe no more than a 4-week (28-day) supply, with no automatic refills or telephone prescriptions
- Return to Celgene all THALOMID® (thalidomide) that is returned by patients. Shipping fees will be paid by Celgene Corporation. Call 1-888-423-5436

Please fill out the spaces below completely.

Prescriber Name _____ Degree: MD/DO/PA/NP Other: Fellow/Medical Resident
(Please print name as it appears on your prescription pad)

Specialty _____

DEA No. _____ Social Security No. (if no DEA)_____

Please indicate which office(s) will receive *S.T.E.P.S.*® materials and updates:

☐ Primary Office Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Email Address _____

☐ Secondary Office Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Email Address _____

I understand that if I fail to comply with <u>all</u> requirements of the *S.T.E.P.S.*® program, my prescriptions for THALOMID® (thalidomide) may not be honored at registered pharmacies.

Prescriber Signature _____ Date _____

Return this card to the Celgene Customer Care Center via mail or by fax (1-888-432-9325).

THALOMID® (thalidomide) Capsules

Celgene

Fold, peel strip, and seal.

NO POSTAGE
NECESSARY
IF MAILED
IN THE
UNITED STATES

BUSINESS REPLY MAIL
FIRST-CLASS MAIL PERMIT NO. 101 SUMMIT NJ

POSTAGE WILL BE PAID BY ADDRESSEE

CELGENE CORPORATION
CELGENE CUSTOMER CARE CENTER
86 MORRIS AVENUE
SUMMIT NJ 07901-9920

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

Important Information for Men and Women Taking

WARNINGS:

1. 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 (REGARDLESS OF STRENGTH)] 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.

2. VENOUS THROMBOEMBOLIC EVENTS.

THE USE OF THALOMID® (thalidomide) IN MULTIPLE MYELOMA RESULTS IN AN INCREASED RISK OF VENOUS THROMBOEMBOLIC EVENTS, SUCH AS DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLUS. THIS RISK INCREASES SIGNIFICANTLY WHEN THALIDOMIDE IS USED IN COMBINATION WITH STANDARD CHEMOTHERAPEUTIC AGENTS INCLUDING DEXAMETHASONE. IN ONE CONTROLLED TRIAL, THE RATE OF VENOUS THROMBOEMBOLIC EVENTS WAS 22.5% IN PATIENTS RECEIVING THALIDOMIDE IN COMBINATION WITH DEXAMETHASONE COMPARED TO 4.9% IN PATIENTS RECEIVING DEXAMETHASONE ALONE (*P*=0.002). PATIENTS AND PHYSICIANS ARE ADVISED TO BE OBSERVANT FOR THE SIGNS AND SYMPTOMS OF THROMBOEMBOLISM. PATIENTS SHOULD BE INSTRUCTED TO SEEK MEDICAL CARE IF THEY DEVELOP SYMPTOMS SUCH AS SHORTNESS OF BREATH, CHEST PAIN, OR ARM OR LEG SWELLING. PRELIMINARY DATA SUGGEST THAT PATIENTS WHO ARE APPROPRIATE CANDIDATES MAY BENEFIT FROM CONCURRENT PROPHYLACTIC ANTICOAGULATION OR ASPIRIN TREATMENT.

WARNING: FOR YOUR HEALTH AND SAFETY, PLEASE READ THIS BOOKLET CAREFULLY. ALSO, BE SURE YOU UNDERSTAND WHAT YOUR DOCTOR HAS TOLD YOU ABOUT THALOMID® (thalidomide) BEFORE STARTING TREATMENT.

Table of Contents

Before taking THALOMID® (thalidomide), you must:

- Understand that THALOMID® (thalidomide) can cause severe birth defects.
- Know how to prevent pregnancy, if you are a woman.
- Understand that you must use latex condoms EVERY TIME you have sexual contact with a woman who can become pregnant, if you are a man.
- Understand that you must NEVER share this drug with friends, relatives, or anyone else.
- Know about other health problems called "side effects."
- Understand that you must NEVER donate blood or sperm while you are taking THALOMID® (thalidomide).

How to Use This Booklet

For easy reading, this booklet has four sections. If you are a woman, read all of Sections 1, 2, and 4. If you are a man, read all of Sections 1, 3, and 4.

This booklet contains important information about THALOMID® (thalidomide), but may not answer all of your questions about the drug. If you need more information, ask your doctor before starting treatment.

When you see this symbol, it means the information nearby is an important reminder NOT TO GET PREGNANT. THALOMID® (thalidomide) can cause severe birth defects.

Section 1: Information for All Patients

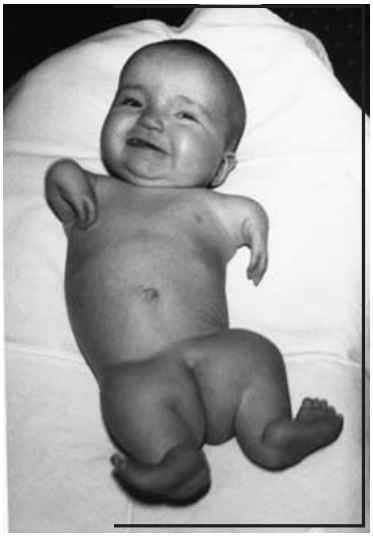
General guidelines for taking THALOMID® (thalidomide)

- THALOMID® (thalidomide) MUST NEVER be used by pregnant women or women who are able to become pregnant and are not using the required two methods of birth control. Just ONE CAPSULE taken by a pregnant woman can cause severe birth defects.
- Men taking THALOMID® (thalidomide) must use latex condoms every time they have sexual contact with women who can become pregnant since THALOMID® (thalidomide) is found in semen or sperm. The risk to the fetus from the semen of male patients taking THALOMID® (thalidomide) is unknown.
- This medicine is ONLY for you. DO NOT SHARE IT WITH ANYONE, even someone who has symptoms like yours. It must be kept out of the reach of children and should never be given to women who are able to become pregnant.
- Contact your doctor immediately if you have any strange or unusual reactions to THALOMID® (thalidomide).
- Keep THALOMID® (thalidomide) in a cool, dry place.
- THALOMID® (thalidomide) does not induce abortion of the fetus and should never be used for contraception.

WARNING
Birth defects
READ THIS SECTION CAREFULLY!

If a woman taking THALOMID® (thalidomide) gets pregnant, her baby will almost certainly have severe birth defects—or may even die. Women taking THALOMID® (thalidomide) MUST NOT become pregnant, and men taking THALOMID® (thalidomide) must not have sexual contact with a woman who can become pregnant without using a latex condom.

If you have sexual contact without birth control for any reason, stop taking THALOMID® (thalidomide) immediately and talk to your doctor. If your doctor is not available, call 1-888-423-5436.



THALOMID® (thalidomide) can cause severe birth defects, including missing or severely deformed legs and arms. These babies often have hands attached directly to their shoulders and feet attached directly to their hips. Photo reprinted by permission.

WARNING
Blood Clots
READ THIS SECTION CAREFULLY!

Events associated with blood clots have been reported in patients taking THALOMID® (thalidomide), especially when used with other cancer drugs. Your healthcare provider may recommend treatment which could help prevent blood clots. Talk to your healthcare provider if you have shortness of breath, chest pains, or arm or leg swelling.

WARNINGS
Other medical problems

Warnings for all patients:

THALOMID® (thalidomide) can cause other health problems called "side effects," including:

- **Drowsiness:**
  THALOMID® (thalidomide) often causes drowsiness. If you are drowsy, you should not operate machinery or drive a car while taking THALOMID® (thalidomide).

- **Nerve damage:**
  Nerve damage is a common and potentially severe side effect that may be irreversible. Arms, hands, legs, and feet may tingle, hurt, or feel numb. If so, stop taking THALOMID® (thalidomide) and call your doctor right away.

Precaution

Do not drink alcohol or take any other medicines that may make you sleepy without consulting your doctor.

Do not open or unnecessarily handle THALOMID® (thalidomide) capsules. If a broken capsule (or the powder in the capsule) comes in contact with your skin, wash the area with soap and water.

- **Allergic reaction:**
  If you have a red, itchy rash, stop taking THALOMID® (thalidomide) and call your doctor right away. You may also have a fever or fast heartbeat.
- **Dizziness:**
  If you feel dizzy, sit upright for a few minutes prior to standing up from a lying down or sitting position.

ANY OF THESE SIDE EFFECTS SHOULD BE REPORTED TO YOUR DOCTOR IMMEDIATELY!

Ask your doctor about other side effects associated with THALOMID® (thalidomide).

Section 2: Facts for Women

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 (REGARDLESS OF STRENGTH)] TAKEN BY A PREGNANT WOMAN DURING HER PREGNANCY CAN CAUSE SEVERE BIRTH DEFECTS. BECAUSE THALIDOMIDE IS PRESENT IN THE SEMEN OF MALE PATIENTS, MALES RECEIVING THALIDOMIDE MUST ALWAYS USE A LATEX CONDOM DURING SEXUAL CONTACT WITH WOMEN OF CHILDBEARING POTENTIAL EVEN IF HE HAS UNDERGONE A SUCCESSFUL VASECTOMY.

Before treatment:

- You must sign a Patient-Physician Agreement Form that says you understand the risk of birth defects, and that you agree not to become pregnant while taking THALOMID® (thalidomide).

- Remember that this medicine is ONLY for you. YOU MUST NOT SHARE IT with ANYONE, even someone who has symptoms like yours. It must be kept out of the reach of children and should never be given to women who are able to have children.
- If there is ANY chance that you can get pregnant you must begin **TWO** methods of birth control 4 weeks BEFORE you start taking THALOMID® (thalidomide).
- Your doctor must give you a pregnancy test within the 24 hours before you begin taking THALOMID® (thalidomide). **If you are pregnant, YOU CANNOT TAKE** THALOMID® (thalidomide).
- You will have pregnancy tests before and during treatment, even if you agree not to have sexual contact.
- You will be given information about the following acceptable birth control methods:

Highly effective methods

- Intrauterine device (IUD)
- Hormonal (birth control pills, hormonal patches, injections, or implants)
- Tubal ligation (tubes tied)
- Partner's vasectomy

Additional effective methods

- Latex condom
- Diaphragm
- Cervical cap

Remember: You must use at least one highly effective method and one additional effective method AT THE SAME TIME. However, your doctor may recommend that you use two barrier methods for medical reasons.

Talk to your doctor to make sure that other medicines or supplements you are taking do not interfere with your hormonal birth control method. Some medicines and herbal supplements, such as St. John's Wort, can prevent hormonal birth control methods from working properly. You may be required to stop taking these medicines or supplements 1 month before starting THALOMID® (thalidomide) if using a hormonal birth control method.

REMEMBER THAT THE ONLY METHOD OF BIRTH CONTROL THAT IS 100% EFFECTIVE IS NOT HAVING SEXUAL CONTACT AT ALL.

During treatment:

- You must take part in a mandatory, confidential survey that will help make sure that everyone taking THALOMID® (thalidomide) receives, understands, and follows information designed to prevent birth defects.
- If you are able to have children, you must continue to use **TWO** methods of birth control, as discussed with your doctor.
- You must talk to your doctor before changing any birth control methods you have already agreed to use.

If you are able to have children:

- You must have a pregnancy test done by your doctor every week during the first 4 weeks of treatment. You will then have a pregnancy test every 4 weeks if you do not have a period or if your monthly menstrual cycles are regular, or every 2 weeks if your cycles are irregular. You may also need to have a pregnancy test if you miss your period or have unusual menstrual bleeding.
- You will receive no more than a 4-week (28-day) supply of THALOMID® (thalidomide) at a time. You will not receive any THALOMID® (thalidomide) capsules unless testing proves that you are not pregnant. A new prescription is required for further dispensing.
- If you have sexual contact without birth control or if, for any reason, you think you may be pregnant, you must IMMEDIATELY stop taking THALOMID® (thalidomide) and tell your doctor. If your doctor is not available, call 1-888-423-5436.
- If you get pregnant, you must IMMEDIATELY stop taking THALOMID® (thalidomide). Contact your doctor immediately to discuss your pregnancy. If you do not have an obstetrician, your doctor will refer you to one for care and counseling.
- You must not breast-feed a baby while you are being treated with THALOMID® (thalidomide).
- You must NEVER donate to a blood bank while you are being treated with THALOMID® (thalidomide).
- You should be examined by your doctor for nerve damage every month for 3 months after beginning treatment and periodically thereafter. Tests for nerve damage are simple and are not painful.

After treatment:

- You must continue to use the same **TWO** methods of birth control for 4 weeks after you receive your last dose of THALOMID® (thalidomide).

Section 3: Facts for Men

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 (REGARDLESS OF STRENGTH)] TAKEN BY A PREGNANT WOMAN DURING HER PREGNANCY CAN CAUSE SEVERE BIRTH DEFECTS. BECAUSE THALIDOMIDE IS PRESENT IN THE SEMEN OF MALE PATIENTS, MALES RECEIVING THALIDOMIDE MUST ALWAYS USE A LATEX CONDOM DURING SEXUAL CONTACT WITH WOMEN OF CHILDBEARING POTENTIAL EVEN IF HE HAS UNDERGONE A SUCCESSFUL VASECTOMY.

Before treatment:

- You must sign a Patient-Physician Agreement Form that says you understand the risk of birth defects and that you agree to NEVER have sexual contact with a woman unless you use a latex condom (read Section 1).
- Remember that this medicine is ONLY for you. You CANNOT share it with ANYONE, even someone who has symptoms like yours. It must be kept out of the reach of children and should never be given to women who are able to have children.

During treatment:

- You must take part in a mandatory, confidential survey that will help make sure that everyone taking THALOMID® (thalidomide) receives, understands, and follows information in the survey designed to help prevent birth defects. Men must participate in the survey because having sexual contact without a latex condom with a woman who can become pregnant or sharing THALOMID® (thalidomide) capsules could result in exposing an unborn baby to the drug.

- While you are taking THALOMID® (thalidomide), you must use a latex condom **every time** you have sexual contact with a woman who can become pregnant and for 4 weeks after you stop taking the drug.
- You must tell your doctor if you have sexual contact with a woman who can become pregnant without using a latex condom, or if you think for any reason that your partner may be pregnant. If your doctor is not available, call 1-888-423-5436.

REMEMBER THAT THE ONLY BIRTH CONTROL METHOD THAT IS 100% EFFECTIVE IS NO SEXUAL CONTACT AT ALL.

- You must NOT donate to a sperm or blood bank while you are taking THALOMID® (thalidomide) or for 4 weeks after you stop taking the drug.
- You should be examined by your doctor for nerve damage every month for 3 months after beginning treatment and periodically thereafter. Tests for nerve damage are simple and are not painful.

After treatment:

- For 4 weeks after receiving your last dose of THALOMID® (thalidomide), you must use a latex condom EVERY TIME you have sexual contact with a woman who can become pregnant.

Section 4:
A Letter from the Thalidomide Victims Association of Canada (TVAC)

Dear Doctor/Patient:

Have you ever met someone who was born disabled after exposure to thalidomide?

We have. In fact, we are *thalidomiders* — the name we have adopted to describe the surviving children of mothers who were prescribed thalidomide during their pregnancy as a sedative or for nausea and other symptoms of "morning sickness."

You've undoubtedly seen the **dramatic photographs of babies with severe birth defects** caused when thalidomide is taken EVEN ONCE by a pregnant woman. You know the risks!

The **Thalidomide Victims Association of Canada** (TVAC) was formed to meet the needs of the approximately 125 thalidomiders alive in Canada today, and to aid the surviving 10 thalidomiders living in the United States. Of the 10,000 to 12,000 children born with thalidomide deformities around the world in the early sixties, 5,000 survive today. No one will ever know how many children were miscarried or were stillborn because of thalidomide.

TVAC exists as a survivors group to determine and find solutions to the ongoing problems we face. TVAC has also undertaken a mandate of monitoring the responsible use of thalidomide and ensuring the tragedy of the past *never happens again*.

Because of our own personal traumas, and those of our families, we have always stated that we can never accept a world with thalidomide in it.

However, as we know first-hand how people may suffer, we also concede that no one should suffer needlessly. If thalidomide can extend a life, or offer a better quality of life to people with debilitating or chronic illnesses, then we are forced to accept the fact that thalidomide use may be their choice.

As well, we are forced to prefer the regulated use of thalidomide over the alternative:

> *One thalidomide baby born out of ignorance is far worse than one born out of a legitimate attempt to regulate and control the distribution process of this drug.*

Since you may soon be involved in prescribing or taking thalidomide, we need for you to be **fully aware of the power you have …**

- the responsibility to see that you **fully understand the risks thalidomide poses …**
- the **commitment** to do whatever it takes to make sure that NOT EVEN ONE woman loses a child due to thalidomide.

We were as surprised as anyone when the people at Celgene Corporation, makers of THALOMID® (thalidomide), sought the opinions and input of those of us at TVAC

concerning the use of thalidomide in the United States. We felt it was a respectful step in the right direction that our feelings, opinions, and knowledge were being considered.

We are also consoled to know that Celgene Corporation has instituted a comprehensive program to help physicians and pharmacists inform patients about side effects and risks and ensure that they are aware of precautions they must take before, during and after therapy.

The **System for Thalidomide Education and Prescribing Safety** (***S.T.E.P.S.***®) is a multifaceted program developed to help ensure that fetal exposure to THALOMID® (thalidomide) does not occur. All of the materials you need to comply with this system are enclosed.

Meanwhile, we make you one promise:

The Thalidomide Victims Association of Canada will continue to watch the progression of events where thalidomide use is concerned.

We have to!

For further information regarding the history of thalidomide or the status of survivors today, please feel free to contact us.

Sincerely,

Randolph Warren
Chief Executive Officer
Thalidomide Victims
Association of Canada

Giselle Cole
Past President
Thalidomide Victims
Association of Canada

Head Office

Thalidomide Victims Association of Canada
Centre Commercial Joseph Renaud
6830 Boul. Joseph Renaud, Suite 211
Montreal, Quebec, Canada
H1K 3V4

Phone: (514) 355-0811
Fax: (514) 355-0860

WARNING to patients taking THALOMID® (thalidomide) Capsules

Attention Women:

Do NOT take THALOMID® (thalidomide) if you are pregnant, if you are breast-feeding, or if you are able to become pregnant and are not using the required two forms of birth control.

Attention Men:

You must use a latex condom EVERY TIME you have sexual contact with a woman who can become pregnant.

If you have any questions, call 1-888-423-5436

All Patients:

Unused drug should be returned to Celgene for disposal. Call 1-888-423-5436.

Celgen

Celgene Corporation
86 Morris Avenue
Summit, New Jersey 07901

 Printed in U.S.A. 02/07 THA05024R1

Healthcare Professional Adverse Drug Experience Reporting Procedure

Celgene is committed to ensuring patient safety through the monitoring of Adverse Drug Experiences associated with the use of THALOMID®.

Please report adverse drug experiences that are suspected to be associated with the use of THALOMID® and any suspected pregnancy occurring during the treatment with THALOMID® to Celgene using any of the following methods:

Reporting to Celgene:

- Email: drugsafety@celgene.com
- Telephone: 908-673-9667
- Toll Free: 1-800-640-7854 (Global Drug Safety & Risk Management) or 1-888-423-5436 (Customer Care Center)
- Fax: 908-673-9115
- Mail: Global Drug Safety & Risk Management, Celgene Corporation, 86 Morris Avenue, Summit, NJ 07901

Reporting to FDA:

Adverse drug experiences that are suspected to be associated with the use of THALOMID® and any suspected pregnancy during the treatment with THALOMID® may also be reported to the FDA MedWatch Reporting System using any of the following methods:

- Online at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm
- Telephone: 1-800-332-1088
- Fax: 1-800-332-0178
- Mail to: MedWatch 5600 Fishers Lane, Rockville, MD 20852-9787

THALOMID® (thalidomide) Pregnancy Exposure Registry

Version 1.2

Celgene Corporation
86 Morris Ave.
Summit, NJ 07901

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LIST OF FIGURES

1. INTRODUCTION

Thalidomide was introduced in West Germany by Chemie Grunenthal in the 1950s, and was used widely as a sedative and as an anti-inflammatory agent outside the United States. Thalidomide was withdrawn from the market in 1961 because of its teratogenic effects, notably phocomelia, which became known (McBride 1961). Thalidomide was never released in the United States as a sedative or marketed for any indication prior to the discovery of its teratogenic effects.

The FDA approved THALOMID® (thalidomide) capsules for U.S. prescription market availability on 16 Jul 1998. Thalidomide is indicated for the acute treatment of cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL). Thalidomide is not indicated as monotherapy for ENL in the presence of moderate to severe neuritis. Thalidomide is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence. On 25 May 2006, the FDA granted accelerated approval for thalidomide in combination with dexamethasone for the treatment of multiple myeloma.

1.1. *S.T.E.P.S.*® Program

Because of the known teratogenic effects of thalidomide and in an effort to prevent to the greatest extent possible any chance of fetal exposure to thalidomide, THALOMID® (thalidomide) is approved for marketing only under a special restricted distribution program approved by the FDA. Under this program, the System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*®), only prescribers and pharmacists registered with the program are allowed to prescribe and dispense thalidomide. In addition, patients must be advised of, agree to, and comply with the requirements of the S.T.E.P.S. program. To monitor patient compliance with the *S.T.E.P.S.*® program, all patients must complete the *S.T.E.P.S.*® program and participate in a mandatory and confidential surveillance registry.

In the *S.T.E.P.S.*® program, a female patient of childbearing potential (FPCBP) is defined as a sexually mature female who has not undergone a hysterectomy, bilateral oophorectomy, or who has not been postmenopausal naturally for at least 24 consecutive months (i.e., who has had menses at some time in the preceding 24 consecutive months). Registered FPCBP need to complete a brief, confidential telephone survey monthly before a prescription can be written for the medication. The FPCBP must have a thorough understanding of the need for 2 of the recommended forms of birth control beginning at least 4 weeks before therapy, and continuing during therapy (including any necessary dose interruptions) and for at least 4 weeks following discontinuation of therapy with THALOMID®. The FPCBP must have negative pregnancy tests within 24 hours prior to receiving an initial prescription for THALOMID®. Pregnancy tests must be sensitive to 50mIU/mL. A pregnancy test is to be performed weekly during the first 4 weeks, then repeated every 4 weeks in FPCBP with regular menstrual cycles. If menstrual cycles are irregular, testing should occur every 2 weeks. In the event of pregnancy, the FPCBP should discontinue THALOMID®. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her pregnancy test or in her menstrual bleeding. All cases of pregnancy should be reported to FDA MedWatch at 1-800-FDA-1088 and to Celgene at 1-888-423-5436.

2. OBJECTIVE

Celgene is committed to investigating any reports of possible fetal exposure to THALOMID® (thalidomide) whether it is the patient or the patient's partner.

The objectives of the THALOMID® Pregnancy Exposure Registry are:

- to monitor pregnancy outcomes (should one occur) in female patients of childbearing potential and female partners of patients who are exposed to THALOMID® and
- to understand the root cause for the pregnancy.

3. METHODS

Pregnancy is identified as any of the following:

- Pregnancy of a patient
- Pregnancy of a female partner of a patient taking THALOMID®

Reports of pregnancy may be received from the *S.T.E.P.S.*® program in the United States, Celgene Pregnancy Prevention Plan programs in the rest of the world (ROW), voluntary survey from Covance Inc., company representatives, clinical trials (US and ROW), or directly from consumer and health care professionals. Specifications for handling pregnancy reports are included in every Celgene study protocol. All reports of pregnancy in a female patient or partner of patient will be actively monitored. Contact information of health care providers and patients will be retrieved from United States Risk Management System (US RMS) database for reports from the commercial environment and from Celtrak (repository of study information) for reports from clinical trials. Health care providers (HCP; clinical trial investigator, prescriber, obstetrician, neonatologist, pediatrician) will be contacted to obtain pregnancy background, pregnancy outcome, pregnancy follow-up and infant outcome information; patients and male patients of pregnant partners will be contacted (when appropriate) to obtain pregnancy information to the extent permitted by local regulations/laws will permit. A letter with the Pregnancy Background Form will be sent initially to the health care provider (prescriber, clinical trial investigator, and obstetrician) and a letter with the Pregnancy Follow-up Form will be sent every trimester or until the outcome is known. A letter with the Pregnancy Form for patient or male patient of pregnant partner will be sent (when appropriate) within 30 days after a report of a confirmed pregnancy. A letter with the Pregnancy Outcome Form for HCP (prescriber, clinical trial investigator, obstetrician, neonatologist, pediatrician) will be sent within 30 days after expected delivery. A letter with the Pregnancy Outcome Form for patient/male patient of partner will be sent (when appropriate) within 30 days after expected delivery. A letter with the Infant Follow-up Form will be sent to the pediatrician or primary care physician every quarter until the infant is a year old.

All pregnancy cases are entered in the Global Drug Safety database. The Drug Safety Specialist (DSS) or designee will process the completed forms and follow-up with the HCP and patient or male patient of pregnant partner.

The following forms will be used to monitor the pregnancy and pregnancy outcome:

- Pregnancy Background Form for HCP,
- Pregnancy Follow-up Form for HCP,
- Pregnancy Outcome Form for HCP,
- Pregnancy Background Form for Patient or Male Patient of Pregnant Partner
- Pregnancy Outcome Form for Patient or Male Patient of Pregnant Partner, and
- Infant Follow-up Form for Primary Care Physician or Pediatrician.

The Pregnancy Background Form for Patient or Male Patient of Pregnant Partner will be utilized for the root cause analysis of pregnancy. The letters and the forms are found in Appendix 1 and the definition of terms is found in Appendix 2.

The processes are presented in Figure 1, Figure 2 and Figure 3.

3.1. Pregnancy/Pregnancy Background

3.1.1. Health Care Providers

- When a pregnancy is reported, the Drug Safety Specialist (DSS) or designee will make an outbound call to the reporter to verify the pregnancy. If there is no response, the DSS or designee will make another outbound call to the reporter to verify the pregnancy.
- If the pregnancy is verified, the DSS will generate a letter and a Pregnancy Background Form that will be sent to the health care provider (HCP; prescriber, clinical trial investigator, obstetrician, primary care physician).
- If no response is received within 30 days, the letter and Pregnancy Background Form will be resent.
- If there is no response to the second letter within 30 days, an outbound call will be made to the HCP (prescriber, clinical trial investigator, obstetrician, primary care physician) requesting that the Pregnancy Background Form be completed.
- If there is no response to the outbound call from the obstetrician/primary care physician within 30 days, all contacts and attempts will be documented in the case.
- If there is no response to the outbound call from the clinical trial investigator, the clinical study manager will be contacted to assist in obtaining the response from the clinical trial investigator.
- If there is no response to the outbound call from the prescriber within 30 days, he or she will be flagged. When the flagged prescriber request for a prescription authorization, the call will be directed to the DSS or designee who will remind the prescriber to complete the Pregnancy Background Form.
- If there is no response within 30 days, the DSS or designee will document all contacts and attempts. If the completed Pregnancy Background Form is received, the DSS or designee will unflag the Prescriber.
- The DSS or designee will process the completed Pregnancy Background Form.

3.1.2. Patient and Male Patient of Pregnant Partner

- A letter and a Pregnancy Background Form for patient and male patient of pregnant partner will be sent (when appropriate) within 30 days after a report of confirmed pregnancy to patients registered in the S.T.E.P.S.® program. The letter and the form for patient and male patient of pregnant partner will be sent to the clinical trial investigator for completion of the study subject at the next study visit. The

Pregnancy Background Form will collect information for the root cause analysis of pregnancy.

- If no response is received within 30 days, the letter and Pregnancy Background Form will be resent.
- If there is no response to the second letter within 30 days, an outbound call will be made to the patient/male patient of pregnant partner for patients registered in the S.T.E.P.S.® program requesting that the Pregnancy Background Form be completed and to the clinical trial investigator to remind the study subject to complete the form at the next study visit.
- If there is no response to the outbound call from the patient/male patient of pregnant partner within 30 days, the study manager will be contacted to assist in obtaining the response.
- If there is no response to the outbound call from the patient/male patient of pregnant partner within 30 days, all contacts and attempts will be documented in the case.
- The DSS or designee will process the completed Pregnancy Background Form.

3.2. Pregnancy Follow-up

- A Pregnancy Follow-up Form will be sent to the obstetrician/primary care physician every trimester or until the outcome is known.
- If the obstetrician/primary care physician does not respond within 30 days, the letter and Pregnancy Follow-up Form will be resent.
- If there is no response to the second letter, an outbound call will be made to the obstetrician/primary care physician requesting the completion of the Pregnancy Follow-up Form.
- If no response is received within 30 days, all contacts and attempts will be documented in the case.
- The DSS or designee will process the completed Pregnancy Follow-up Form.

3.3. Pregnancy Outcome

3.3.1. Health Care Providers

- For confirmed pregnancies, Pregnancy Outcome Form for HCP (prescriber, clinical trial investigator, obstetrician, neonatologist, pediatrician, primary care physician) will be sent within 30 days after the expected date of delivery.
- If the HCP (prescriber, clinical trial investigator, obstetrician, neonatologist, pediatrician, primary care physician) does not respond within 30 days, the letter and Pregnancy Outcome Form will be resent.
- If there is no response to the second letter, an outbound call will be made to the HCP (prescriber, clinical trial investigator, obstetrician, neonatologist, pediatrician, primary care physician) requesting the completion of the Pregnancy Outcome Form.

- If there is no response from the clinical trial investigator, the study manager will be contacted to assist in obtaining the response.
- If there is no response from the obstetrician/neonatologist/pediatrician/primary care physician/clinical trial investigator within 30 days, all contacts and attempts will be documented in the case.
- If there is no response from the Prescriber within 30 days, the prescriber will be flagged. When the flagged prescriber request for a prescription authorization, the call will be directed to the DSS or designee who will remind the prescriber to complete the Pregnancy Outcome Form.
- If there is no response within 30 days, the DSS or designee will document all contacts and attempts. If the completed Pregnancy Outcome Form is received, the DSS or designee will unflag the Prescriber.
- The DSS or designee will process the completed Pregnancy Outcome Form.

3.3.2. Patient and Male Patient of Pregnant Partner

- A Pregnancy Outcome Form for patient and male patient of pregnant partner will be sent (when appropriate) within 30 days after the expected date of delivery.
- If the patient and male patient of pregnant partner do not respond within 30 days, the letter and Pregnancy Outcome Form will be resent.
- If there is no response to the second letter, an outbound call will be made to the patient and male patient of pregnant partner requesting the completion of the Pregnancy Outcome Form.
- If no response is received within 30 days, all contacts and attempts will be documented in the case.
- The DSS or designee will process the completed Pregnancy Outcome Form.

3.4. Infant Follow-up

- The DSS or designee will send a letter and an Infant Follow-up Form to the primary care physician or pediatrician quarterly until the infant is a year old. The first letter will be sent 3 months after birth.
- If there is no response within 30 days, the DSS or designee will re-send the letter and the Infant Follow-up Form.
- If there is no response to the second letter, an outbound call will be made to the primary care physician or pediatrician requesting the completion of the Infant Follow-up Form.
- If no response is received within 30 days, all contacts and attempts will be documented in the case.
- The DSS or designee will process the completed Infant Follow-up Form.

4. DATA ANALYSIS

Descriptive statistics will be the primary approach for summarizing data from the pregnancy exposure registry.

Subjects' age, duration of thalidomide treatment, and weeks of gestational age at exposure will be summarised using descriptive statistics for continuous variables, while gender, indication for thalidomide use, concomitant medications, type of delivery, pregnancy outcome, obstetrical history, adverse events during pregnancy, fetal outcome, infant status, and cytogenetic abnormalities will be summarised with descriptive statistics appropriate for categorical data. The information will be separately provided for female patients and for male patients and their pregnant partners as appropriate for the variable of interest.

The pregnancy proportion for female patient of childbearing potential (FPCBP) will be determined by dividing the total number of FPCBP experiencing at least one pregnancy over the total FPCBP population. The pregnancy proportion will be stratified by prescribing environment (e.g., patients exposed to commercially marketed thalidomide, patients exposed to thalidomide in clinical trials under IND applications]. Because of the unique denominator data available in the United States, these analyses will be conducted separately for patients in the RevAssist® program. Patients with more than one exposed pregnancy will be tabulated.

The Pregnancy Background Form completed by the patient or male patient of pregnant partner will be utilized to analyze root cause for the pregnancy. The forms of birth control; unprotected sex; reasons for unprotected sex; receipt, reading, and understanding of the medication guide, source of knowledge about contraception, and understanding of the risk of pregnancy during thalidomide use will be summarized with descriptive statistics.

The CDC birth defects code list will be used for classifying any reported congenital anomalies.

5. INDIVIDUAL CASE REPORTS

Initial pregnancy cases must be reported (notification) to the FDA within 24 hours of receipt followed by a 15-day alert report. Any follow-up information received must be submitted as a follow-up 15-day alert report.

For all Celgene products where there is a regulatory commitment for 24-hour notification (i.e, lenalidomide, thalidomide) or a requirement in the clinical study protocol for immediate notification, all Celgene personnel, including affiliates and licensed partners, shall inform Global Drug Safety or the appropriate Celgene Drug Safety department worldwide **IMMEDIATELY** by a telephone call followed by electronic transmission (email or facsimile) of a serious adverse event report of any possible exposure of a pregnant woman to the Celgene product.

6. STATUS REPORTS

The status report will be included in the THALOMID® periodic safety report. The status report will include the following:

- Number of pregnancies in patients and partners of patients with outcome known (stratified by live birth, spontaneous abortions, elective terminations, fetal deaths/stillbirths)
- Number of pregnancies with outcome pending
- Number of pregnancies lost to follow-up
- Pregnancy proportions for FPCBP patients and for male patients, stratified by prescribing environment
- Number of females of childbearing potential exposed for postmarketing and clinical trials (US and ROW*) during the time period
- Number of males exposed for postmarketing and clinical trials (US and ROW*) during the time period

*Note: *S.T.E.P.S.*® is unique to the United States. In other countries where THALOMID® is marketed, such controlled distribution may not be possible because of legal restraints. Hence, accurate data on patient demographics will not be available.

For pregnancies with known outcome, the status report will include line listings and summaries of:

- Demographics, obstetrical and medical history of mothers
- Weeks of gestational age at exposure
- Type, dose and duration of exposure
- Weeks of gestational age at completion or termination of pregnancy
- For live births and deaths/stillbirths, whether multiple birth, small for gestational age, pre-term delivery and congenital anomalies or other fetal abnormalities
- For spontaneous abortions and elective terminations, abnormalities in products of conception

7. REGISTRY DISCONTINUATION

The pregnancy registry will be evaluated annually to determine if the feasibility of collecting information has diminished to unacceptable levels because of low exposure rates or loss to follow-up

8. REFERENCES

CDC. Metropolitan Atlanta Congenital Defects Program Procedure Manual, 1993:A32-A100, (77) 488-7160.

EMEA Committee for Medicinal Products for Human Use: *Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation Data.* London, UK. 14 Nov 2005.

Food and Drug Administration. *Guidance for Industry Establishing Pregnancy Exposure Registries.* Rockville, Md. August 2002.

Investigator's Brochure for Thalidomide. Summit, NJ:Celgene Corporation, 06 Mar 2007.

THALOMID® [Full Prescribing Information]. Summit, NJ: Celgene Corporation; 2005.

S.T.E.P.S.® Starter Kit

Figure 1: Pregnancy Background and Follow -Up Process Flow -HCP

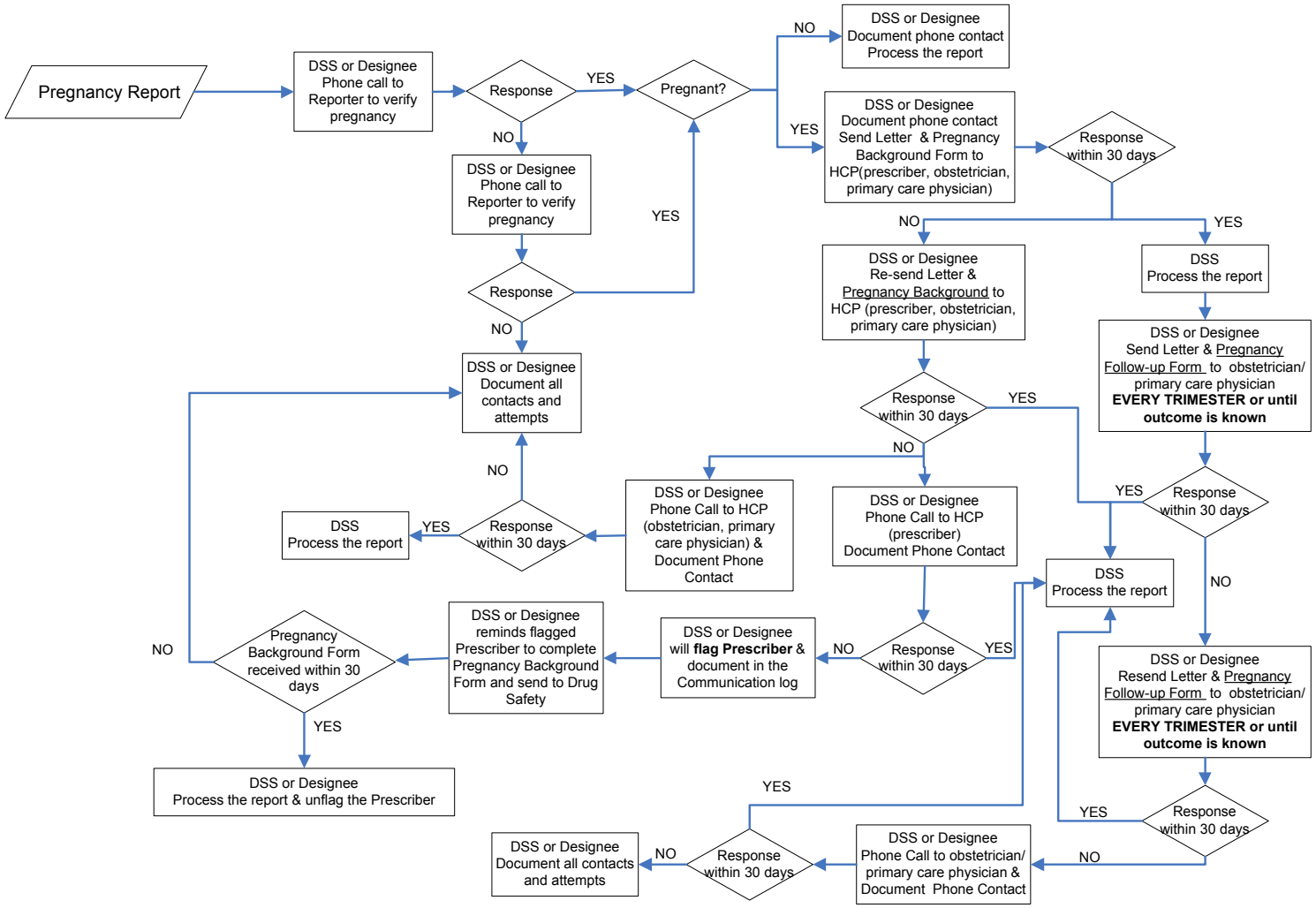


Figure 2: Pregnancy Outcome and Infant Follow -Up Process Flow -HCP

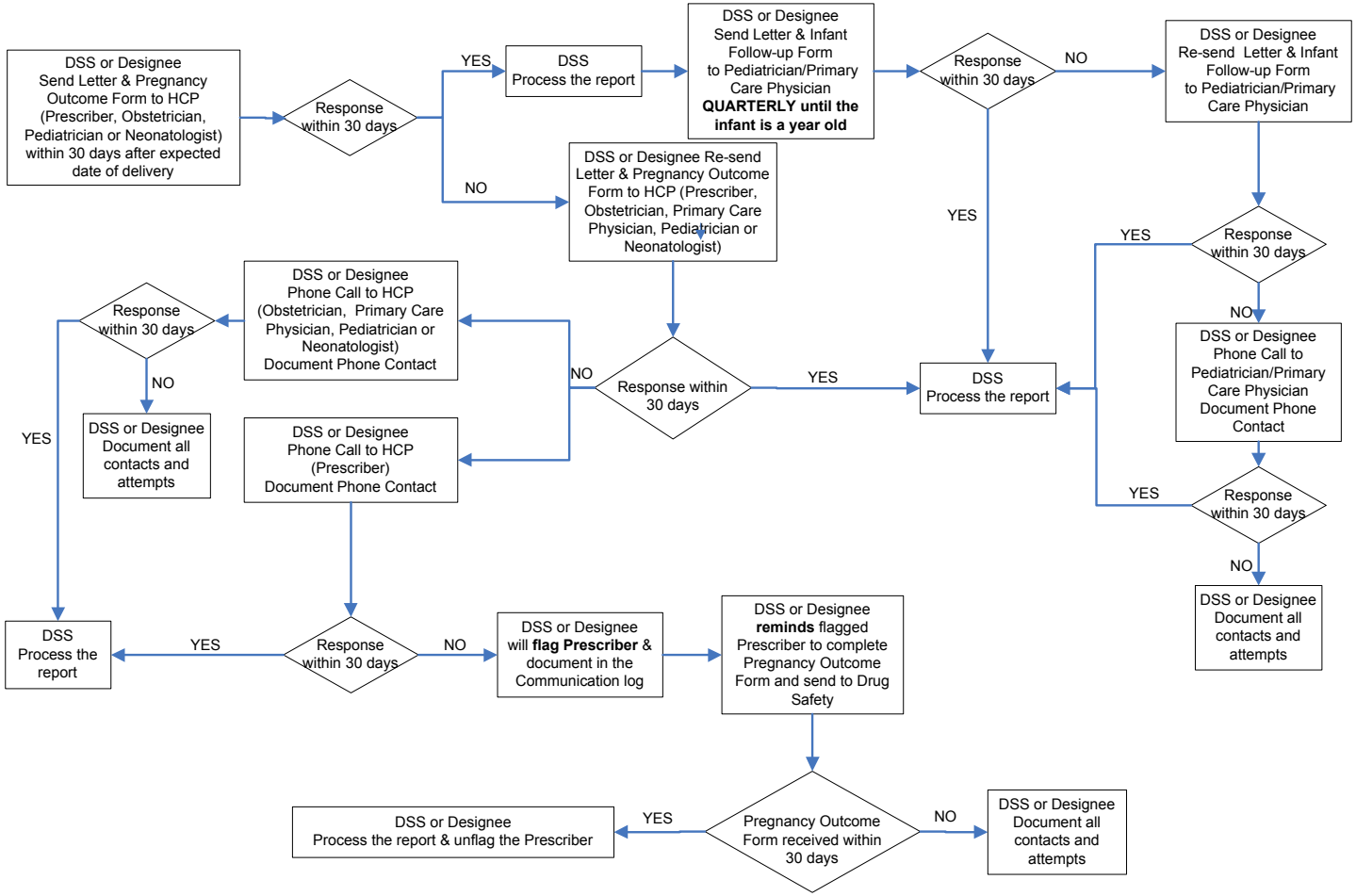
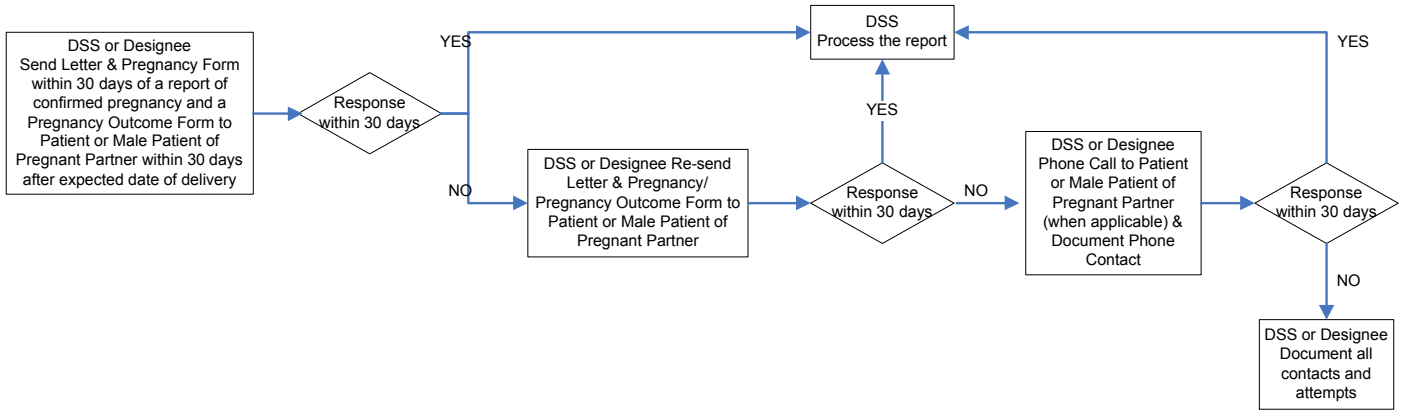


Figure 3: Pregnancy/Pregnancy Outcome Process Flow -Patient and Male Patient of Pregnant Partner



APPENDIX 1: PREGNANCY LETTERS AND QUESTIONNAIRES

Name, MD [Prescriber/Clinical trial investigator/
Obstetrician/Pediatrician/Neonatologist/Primary Care Physician)
Attn: Name
Address:

DDMMYYYY

Re: Patient Identifier: [patient identifier]
Patient DOB, Patient sex
Drug: [Primary Suspect Product Name]
Our Manufacturer Control No (MCN): [MCN]

Dear Dr. [Selected Reporter]

The Celgene Corporation Drug Safety Department has received a report of a pregnancy regarding your patient [patient identifier].

Celgene is committed to investigating any reports of possible fetal exposure to our products whether it be the patient or patient's partner. In order to perform a thorough evaluation and to meet our regulatory reporting requirements throughout the world, we are interested in obtaining additional details regarding this patient. Please be assured that all information will be treated in the strictest of confidence.

Please complete the enclosed Event-Specific Questionnaire for HCP – Pregnancy Background (Patient or Partner of Patient)/ Event-Specific Questionnaire for HCP - Pregnancy Outcome (Patient or Partner of Patient)/ Event-Specific Questionnaire for HCP - Pregnancy Follow-up (Patient or Partner of Patient)/ Event-Specific Questionnaire for Primary Care Physician or Pediatrician Infant Follow-up, date and sign the form(s) and return to Celgene Drug Safety via mail (self-addressed envelope provided), or FAX to (908) 673-9115. Please provide our Manufacturer Control No. as stated above in all communications regarding this case.

If you are aware that further information will not be available, it would be helpful if you could indicate that to us, including the reason if complete information cannot be provided.

If you have any questions, please do not hesitate to contact me at 1-800-640-7854.

Thank you in advance for your assistance.

Name of Specialist
Title

Name of Patient
Address:

DDMMYYYY

Re: Patient Identifier: [patient identifier]
Patient DOB, Patient sex
Drug: [Primary Suspect Product Name]
Our Manufacturer Control No (MCN): [MCN]

Dear [Patient's Name]

The Celgene Corporation Drug Safety Department has received a report of your [your partner's pregnancy].

Celgene is committed to investigating any reports of possible fetal exposure to our products whether it be the patient or patient's partner. In order to perform a thorough evaluation and to meet our regulatory reporting requirements throughout the world, we are interested in obtaining additional details regarding your [your partner's] pregnancy. Please be assured that all information will be treated in the strictest of confidence.

Please complete the enclosed Event-Specific Questionnaire for Patient or Male Patient of Pregnant Partner – Pregnancy Background/ Event-Specific Questionnaire for Patient or Male Patient of Pregnant Partner – Pregnancy Outcome Form and return to Celgene Drug Safety via mail (self-addressed envelope provided), or FAX to (908) 673-9115.

If you have any questions, please do not hesitate to contact me at 1-800-640-7854.

Thank you in advance for your assistance.

Name of Specialist
Title

Event-Specific Questionnaire for HCP – Pregnancy Background
(Patient or Partner of Patient)
Telephone: (908) 673-9667
Fax: (908) 673-9115
Email: Drugsafety@celgene.com

Reporter Information				
REPORTER NAME:				
ADDRESS:		CITY, STATE, ZIP, COUNTRY:		
PHONE NO.:		FAX NO.:		
Obstetrician Information (Please provide)				
OBSTETRICIAN NAME:				
ADDRESS:		CITY, STATE, ZIP, COUNTRY:		
PHONE NO.:		FAX NO.:		
Patient Information				
PATIENT ID:	DATE OF BIRTH:	ETHNICITY: ☐ WHITE ☐ AFRICAN-AMERICAN ☐ ASIAN ☐ OTHER, SPECIFY:		
Partner of Patient Information ☐ Not applicable				
DATE OF BIRTH:	ETHNICITY: ☐ WHITE ☐ AFRICAN-AMERICAN ☐ ASIAN ☐ OTHER, SPECIFY:			
Patient Treatment Information: THALOMID®				
LOT NO.	EXPIRY DATE:	DOSE:	FREQUENCY:	ROUTE:
START DATE		STOP DATE		
INDICATION FOR USE				
CYTOGENETIC ABNORMALITIES: ☐ NO ☐ YES, IF YES, SPECIFY:				

Current Pregnancy					
Date of last menstrual period:		Estimated Delivery Date:			
Pregnancy Test	*REFERENCE RANGE*	*DATE*			
Urine Qualitative					
Serum quantitative					

Prenatal Tests		
	Date	*Result*
Ultrasound		
Ultrasound		
Ultrasound		
Amniocentesis		
Maternal Serum AFP		

Pregnancy History		
No. of previous pregnancies: Date of last pregnancy:	No. of Full term deliveries:	No. of Pre-term births:
No. of fetal deaths:	No. of living children:	No. of abortions: Elective Spontaneous

Type of delivery: Vaginal:	C-section:	Other:, specify

Did birth defect occur in any previous pregnancy? ☐ No ☐ Yes ☐ Unknown
If Yes, specify

Did a stillbirth or miscarriage occur in any previous pregnancy? No ☐ Yes ☐ Unknown ☒
1) If Yes, in what week of pregnancy did the stillbirth or miscarriage occur? _____ week
2) Was there any birth defect noted? Specify:

MCN:

Relevant Medical History

	Date of Diagnosis		*Date of Diagnosis*
Cancer ☐ No ☐ Yes, if yes, specify _____			

Social History

Alcohol ☐ No ☐ Yes, if yes, amount/unit consumed per day:

Tobacco ☐ No ☐ Yes | IV or recreational drug use ☐ No ☐ Yes, specify

Family History: Congenital Abnormalities ☐ No ☐ Yes, specify:

Medications/Treatments (including herbal, alternative and over the counter medicines and dietary supplements) During Pregnancy

Drug	*Start Date*	*Stop Date/ Continuing*	*Indication*

Adverse Event(s) During Pregnancy

Event(s)	Serious		Serious Criteria[1]	Start Date	Stop Date	Causal Relationship to Celgene Product		
	No	Yes				Yes	No	If No, what medications, disease states etc played a role in the event.

[1] Serious Criteria: **1**) death, **2**) life-threatening, **3**) required inpatient hospitalization or prolongation of existing hospitalization, **4**) a persistent or significant disability/incapacity, **5**) a congenital anomaly/birth defect, **6**) medically significant

Signature of Person Completing this form ..... **Date** .....

MCN:

Event-Specific Questionnaire for Patient or Male Patient of Pregnant Partner–
Pregnancy Background
Telephone: (908) 673-9667
Fax: (908) 673-9115
Email: Drugsafety@celgene.com

Date _____
Name of Patient or Name of Male Patient of Partner _____

For a better understanding of pregnancy among patients or partners of patients on Thalomid® and for further improvement of the *S.T.E.P.S.*® program, please complete the following questions.

1. What forms of birth control have you been using while on THALOMID® before you/your partner got pregnant? Please check all that applies.

☐ IUD

☐ Hormonal (birth control pills, hormonal patches, injections, implants)

☐ Tubal ligation

☐ Partner's vasectomy

☐ Latex condom

☐ Diaphragm

☐ Cervical cap or shield

☐ Spermicide or sponge

☐ Withdrawal

2. Were you or your partner at any time during use of THALOMID® without contraception for even one day?

☐ No, please proceed to Q5

☐ Yes, please answer Q3, Q4, Q5, and Q6

3. How often did you have unprotected sexual intercourse?

☐ multiple times

☐ once a week

☐ once every 2 weeks

☐ once a month

☐ not at all

☐ other, specify _____

4. Why did you or your partner interrupt or stop using contraception?

☐ wanted a child

☐ partner disapproved

☐ side effects

☐ health concerns

☐ inconvenient to use

☐ other, specify _____

5. Where did most of your knowledge about contraception during THALOMID® use come from?

☐ physician who prescribed THALOMID®

☐ *S.T.E.P.S.*® Patient Resource Pack

☐ THALOMID® Medication Guide

☐ Other, specify _____

6. Do you feel you and/or your partner had good understanding of the risk of pregnancy during THALOMID® use?

☐ Yes

☐ No

☐ Don't know

Event-Specific Questionnaire for HCP – Pregnancy Follow-up
(Patient or Partner of Patient)
Telephone: (908) 673-9667
Fax: (908) 673-9115
Email: Drugsafety@celgene.com

Date:	**Period Covered: [Date] to [Date]**
Reporter Information	
REPORTER NAME:	
ADDRESS:	CITY, STATE, ZIP, COUNTRY:
PHONE NO.:	FAX NO.:
Name of Patient or Pregnant Partner of Male Patient	
Current Pregnancy	
Prenatal Tests	

	Date	*Result*
Ultrasound		
Ultrasound		
Ultrasound		
Amniocentesis		
Maternal Serum AFP		
Other tests, specify		

Medications/Treatments (including herbal, alternative and over the counter medicines and dietary supplements) During Pregnancy

DRUG	*START DATE*	*STOP DATE/ CONTINUING*	*INDICATION*

Adverse Event(s) During Pregnancy

Event(s)	SERIOUS		SERIOUS CRITERIA[1]	START DATE	STOP DATE	CAUSAL RELATIONSHIP TO CELGENE PRODUCT		
	NO	YES				YES	NO	If No, what medications, disease states etc played a role in the event.

[1] Serious Criteria: **1**) death, **2**) life-threatening, **3**) required inpatient hospitalization or prolongation of existing hospitalization, **4**) a persistent or significant disability/incapacity, **5**) a congenital anomaly/birth defect, **6**) medically significant

SIGNATURE OF PERSON COMPLETING THIS FORM ..... **DATE** .....

MCN:

Event-Specific Questionnaire for HCP – Pregnancy Outcome
(Patient or Partner of Patient)
Telephone: (908) 673-9667
Fax: (908) 673-9115
Email: Drugsafety@celgene.com

Reporter Information			
REPORTER NAME:			
ADDRESS:		CITY, STATE, ZIP, COUNTRY:	
PHONE NO.:		FAX NO.:	
Patient Information			
PATIENT ID:	DATE OF BIRTH:	ETHNICITY: ☐ WHITE ☐ AFRICAN-AMERICAN ☐ OTHER, SPECIFY:	
Partner of Patient Information ☐ Not applicable			
DATE OF BIRTH:		ETHNICITY: ☐ WHITE ☐ AFRICAN-AMERICAN ☐ OTHER, SPECIFY:	
Pregnancy Outcome			
DATE OF DELIVERY:		GESTATION AGE AT DELIVERY:	

	No	**Yes**	
Normal	☐	☐	
C-section	☐	☐	
Induced	☐	☐	
Ectopic pregnancy	☐	☐	
Elective termination	☐	☐	Date:
Spontaneous abortion (≤20 weeks)	☐	☐	Weeks from LMP:
Fetal death/stillbirth (>20 weeks)	☐	☐	
Were the products of conception examined?	☐	☐	If yes, was the fetus normal? ☐ Yes ☐ No ☐ Unknown If no, describe:

Obstetrics Information			
	No	**Yes**	
Complications during pregnancy	☐	☐	If yes, please specify
Complications during labor/delivery	☐	☐	If yes, please specify
Post-partum maternal complications	☐	☐	If yes, please specify

Fetal Outcome			
	No	**Yes**	
LIVE NORMAL INFANT	☐	☐	
FETAL DISTRESS	☐	☐	
INTRA-UTERINE GROWTH RETARDATION	☐	☐	
NEONATAL COMPLICATIONS	☐	☐	IF YES, PLEASE SPECIFY:
BIRTH DEFECT NOTED?	☐	☐	IF YES, PLEASE SPECIFY:

Sex: ☐ Male ☐ Female	**Birth Weight:** __lbs _ oz. or __ kg	**Length:** _____inches or ___ cm.

Apgar Score:	Unknown:	1 min:	5 min:	10 min:

SIGNATURE OF PERSON COMPLETING THIS FORM **DATE**

MCN:

Event-Specific Questionnaire for Patient or Male Patient of Pregnant Partner–
Pregnancy Outcome
Telephone: (908) 673-9667
Fax: (908) 673-9115
Email: Drugsafety@celgene.com

Date _____
Name of Patient or Name of Male Patient of Partner _____

Please provide the outcome of your or your partner's pregnancy.

☐ Normal baby

☐ Abnormal baby, please specify defect_____

☐ Therapeutic abortion
Please specify any abnormality of the fetus if known: _____

☐ Spontaneous abortion or miscarriage
Please specify any abnormality of the fetus if known: _____

Event-Specific Questionnaire for Primary Care Physician or Pediatrician – Infant Follow-up

Telephone: (908) 673-9667
Fax: (908) 673-9115
Email: Drugsafety@celgene.com

Date: _____
Name of Patient or Name of Male Patient of Partner (Mother)_____
Name of Infant (if known) _____

Please provide information for the period from [**Date]** to [**Date**].

Anomalies Diagnosed Since Initial Report:

_____

☐ None

Developmental Assessment:

☐ Normal

☐ Abnormal, specify _____

Infant Illnesses, Hospitalizations, Drug Therapies:

Infant Illnesses	Hospitalized?	Drug Therapies
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	

SIGNATURE OF PERSON COMPLETING THIS FORM _____ DATE _____

APPENDIX 2: DEFINITIONS

Fetus: covers the whole prenatal development from the conception until birth.

Pregnancy outcome: the end products of pregnancy which include three main categories: fetal death, termination of pregnancy and live birth.

- Fetal death (intrauterine death, in utero death): death prior to complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy; the death is indicated by the fact that after such separation the fetus does not show any evidence of life (WHO ICD 10).
  - Early fetal death (before 20 completed weeks of gestation) comprises ectopic pregnancy and miscarriage
  - Late fetal death (after 20 completed weeks of gestation) – known as stillbirth

Miscarriage: spontaneous abortion, molar pregnancy

Termination of pregnancy (induced abortion, elective abortion): artificial interruption of pregnancy

Live birth: the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy, which, after such separation, breathes or shows any evidence of life (WHO ICD 10)

Gestational age or length: duration of gestation is measured from the first day of the last normal menstrual period. Gestation age is expressed in completed days or completed weeks (e.g., events occurring 280 to 286 days after the onset of the last menstrual period are considered to have occurred at 40 weeks of gestation).

Last menstrual period (LMP): according to international consensus, the gestational age is measured from the first day of the LMP.

Birth weight: the initial weight of the infant at birth

Pre-term baby (previously premature birth): less than 37 completed weeks (less than 259 days) of gestation

Term birth: from 37 to less than 42 completed weeks (259 to 293 days)

Post-term birth: 42 completed weeks or more (294 days or more)

Low birth weight: less than 2,500 gram (up to and including 2,499 g) of body weight of the newborn at birth

Intrauterine growth retardation (small for gestational age): the observed weight of a live born infant or size of a fetus is lower than expected on the basis of gestational age.

THALOMID - thalidomide capsule

THALOMID® PACKAGE INSERT

THALOMID® (thalidomide) Capsules 50 mg, 100 mg, 150 mg & 200mg

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] 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 4 weeks of use, then 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 at 1-888-423-5436. 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 beginning thalidomide therapy, during thalidomide therapy, and for 4 weeks after 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 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 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.

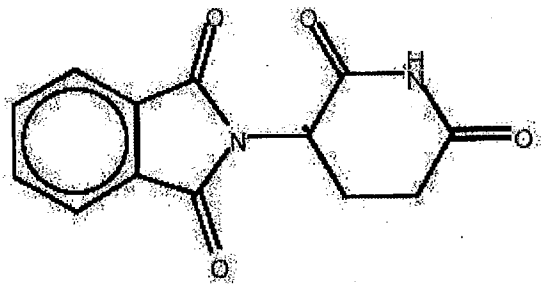
Venous Thromboembolic Events

The use of THALOMID® (thalidomide) in multiple myeloma results in an increased risk of venous thromboembolic events, such as deep venous thrombosis and pulmonary embolus. This risk increases significantly when thalidomide is used in combination with standard chemotherapeutic agents including dexamethasone. In one controlled trial, the rate of venous thromboembolic events was 22.5% in patients receiving thalidomide in combination with dexamethasone compared to 4.9% in patients receiving dexamethasone alone ($p = 0.002$). Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Preliminary data suggest that patients who are appropriate candidates may benefit from concurrent prophylactic anticoagulation or aspirin treatment.

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, 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, 150 mg and 200 mg capsules for oral administration. Active ingredient: thalidomide. Inactive ingredients: 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 150 mg capsule shell contains FD&C blue #2, black iron oxide, yellow iron oxide, titanium dioxide, gelatin, and black and white ink. The 200 mg capsule shell contains FD&C blue #2, titanium dioxide, gelatin, and white ink.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of thalidomide is not fully understood. Thalidomide possesses immunomodulatory, anti-inflammatory and anti-angiogenic properties. Available data from *in vitro* studies and 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 erythema nodosum leprosum (ENL)[3], however, it has also been shown to increase plasma TNF-α levels in HIV-seropositive patients.[7] Other anti-inflammatory and immunomodulatory properties of thalidomide may include suppression of macrophage involvement in prostaglandin synthesis, and modulation of interleukin-10 and interleukin-12 production by peripheral blood mononuclear cells. Thalidomide treatment of multiple myeloma patients is accompanied by an increase in the number of circulating natural killer cells, and an increase in plasma levels of interleukin-2 and interferon-gamma (T cell-derived cytokines associated with cytotoxic activity). Thalidomide was found to inhibit angiogenesis in a human umbilical artery explant model *in vitro*. The cellular processes of angiogenesis inhibited by thalidomide may include the proliferation of endothelial cells.

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. However, the capsules are 90% bioavailable relative to an oral PEG solution. 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%)
			3.5	5.53

200 mg	18.9 (17%)	1.76 (30%)	(57%)	(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 products. 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

impairment have not been determined. In a study of 6 patients with end-stage renal disease, thalidomide (200 mg/day) was administered on a non-dialysis day and on a dialysis day. Comparison of concentration-time profiles on a non-dialysis day and during dialysis where blood samples were collected at least 10 hours following the dose, showed that the mean total clearance increased by a factor of 2.5 during hemodialysis. Because the dialysis was performed 10 hours following administration of the dose, the drug-concentration time curves were not statistically significantly different for days patients were on and off of dialysis. Thus, no dosage adjustment is needed for renally-impaired patients on dialysis.

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

Clinical Study in Multiple Myeloma:

The efficacy of THALOMID® in multiple myeloma was demonstrated in a randomized, multi-center open-label study of 207 newly diagnosed patients. This study randomized symptomatic patients with newly diagnosed multiple myeloma to THALOMID® plus dexamethasone (Thal + Dex; N = 103) versus dexamethasone alone (Dex alone; N=104). The THALOMID® dose was 200 mg daily and the dexamethasone dose was 40 mg orally once daily on days 1-4, 9-12, and 17-20 every 28-days. Each group was treated for four 28-day cycles.

Baseline demographic and disease characteristics for the study population are summarized in Tables 2 and 3 respectively.

Table 2 Baseline Patient Demographics

Characteristic	Thal + Dex (N=103)	Dex alone (N=104)
Age (years)		
Median	65	68
Range	37 – 83	38 – 83
Gender[1]		
Male	53 (51%)	61 (59%)
Female	50 (49%)	42 (40%)
Race[2]		
Caucasian	90 (87%)	90 (87%)
Black	11 (11%)	11 (11%)
Other	1 (1%)	2 (2%)

[1]1Missing information for 1 patient in the Dex alone group
[2]Missing information for 1 patient per arm

Table 3 Baseline Disease Characteristics

Characteristic	Thal + Dex (N=103)	Dex alone (N=104)
Stage (Durie-Salmon), N (%)[1]		
I	14 (13.6%)	17 (16.3%)
II	47 (45.6%)	44 (42.3%)
III	41 (39.8%)	43 (41.3%)
Immunoglobulin Type, N (%)[2]		
IgA	21 (20.4%)	22 (21.2%)
IgG	63 (61.2%)	60 (57.7%)
IgM	0 (0.0%)	1 (1.0%)
Biclonal	0 (0.0%)	1 (1.0%)
Lytic Lesions[3]		
None	28 (27.1%)	14 (13.5%)
1-3 lesions	24 (23.3%)	19 (18.3%)
>3 lesions	34 (33.0%)	41 (39.4%)
Serum Light Chain[4]		
Kappa	59 (57.3%)	53 (51.0%)
Lambda	28 (27.2%)	40 (38.5%)

[1]Missing information for 1 patient in Thal + Dex arm
[2]Missing information for 19 patients in Thal + Dex arm and 20 patients in Dex alone arm
[3]Missing information for 17 patients in Thal + Dex arm and 30 patients in Dex alone arm
[4]Missing information for 16 patients in Thal + Dex arm and 11 patients in Dex alone arm

Response rate was the primary endpoint. Response rates based on serum or urine paraprotein measurements were significantly higher in the combination arm (51.5 % compared with 35.6 % for dexamethasone alone).

Erythema Nodosum Leprosum (ENL)

The primary data demonstrating the efficacy of thalidomide in the treatment of the cutaneous manifestations of moderate to severe ENL are derived from the published medical literature and from a retrospective study of 102 patients treated by the 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 4 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]			Thalidomide	Aspirin
Bull World Health Organization 1971;45:719	92	204	75%	25%
Sheskin *et al.*[11]			Thalidomide	Placebo
Int J Lep1969;37:135	52	173	66%	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 5 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]	4 weeks	9	4/5	0/4
Lep Rev 1971;42:26	6 weeks (crossover)	8	8/8	1/8

Data on the efficacy of thalidomide in prevention of ENL relapse were derived from a retrospective evaluation of 102 patients treated under the auspices of the U.S. Public Health Service. A subset of patients with ENL controlled on thalidomide demonstrated repeated relapse upon drug withdrawal and remission with reinstitution of therapy.

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

Multiple Myeloma

THALOMID® (thalidomide) in combination with dexamethasone is indicated for the treatment of patients with newly diagnosed multiple myeloma.

The effectiveness of THALOMID® is based on response rates (see **CLINICAL STUDIES** section). There are no controlled trials demonstrating a clinical benefit, such as an improvement in survival.

Erythema Nodosum Leprosum

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**), two other effective or highly effective methods may be used.

Women of childbearing potential being treated with thalidomide 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 and then weekly during the first 4 weeks of thalidomide therapy, 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 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 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. The risk to the fetus from the semen of male patients taking thalidomide is unknown.

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

WARNINGS (See BOXED WARNINGS.)

Birth Defects:

Thalidomide can cause severe birth defects in humans. (See **BOXED 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. The risk to the fetus from the semen of male patients taking thalidomide is unknown.

Thrombotic Events:

The use of THALOMID® (thalidomide) in multiple myeloma results in an increased risk of venous thromboembolic events, such as deep venous thrombosis and pulmonary embolus. This risk increases significantly when thalidomide is used in combination with standard chemotherapeutic agents including dexamethasone. In one controlled trial, the rate of venous thromboembolic events was 22.5% in patients receiving thalidomide in combination with dexamethasone compared to 4.9% in patients receiving dexamethasone alone ($p = 0.002$). Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Preliminary data suggest that patients who are appropriate candidates may benefit from concurrent prophylactic anticoagulation or aspirin treatment (See **BOXED WARNINGS**).

Drowsiness and Somnolence:

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

Peripheral Neuropathy:

Thalidomide is known to cause nerve damage that may be permanent. Peripheral neuropathy is a common, potentially severe, side effect of treatment with thalidomide that may be irreversible. Peripheral neuropathy generally occurs following chronic use over a period of months; however, reports following relatively short-term use also exist. The correlation with cumulative dose is unclear. Symptoms may occur some time after thalidomide treatment has been stopped and may resolve slowly or not at all.

Few reports of neuropathy have arisen in the treatment of ENL despite long-term thalidomide treatment. However, the inability clinically to differentiate thalidomide neuropathy from the neuropathy often seen in Hansen's disease makes it difficult to determine accurately the incidence of thalidomide-related neuropathy in ENL patients treated with thalidomide.

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

Dizziness and Orthostatic Hypotension:

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

Neutropenia:

Decreased white blood cell counts, including neutropenia, have been reported in association with the clinical use of thalidomide. Treatment should not be initiated with an absolute neutrophil count (ANC) of <750/mm^3. White blood cell count and differential should be monitored on an 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 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] 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

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 childbearing 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.

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. 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.

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

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.

Patients should be educated about the signs and symptoms of thromboembolism and instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg

swelling.

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 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 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, modafinil, penicillins, rifampin, rifabutin, phenytoin, 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted in male and female rats and mice. No compound-related tumorigenic effects were observed at the highest dose levels of 3,000 mg/kg/day to male and female mice (38-fold greater than the highest recommended daily human dose of 400 mg based upon body surface area [BSA]), 3,000 mg/kg/day to female rats (75-fold the maximum human dose based upon BSA), and 300 mg/kg/day to male rats (7.5-fold the maximum human dose based upon BSA).

Thalidomide was neither mutagenic nor genotoxic in the following assays: the Ames bacterial (*S. typhimurium and E. coli*) reverse mutation assay, a Chinese hamster ovary cell (AS52/XPRT) forward mutation assay, and an *in vivo* mouse micronucleus test.

Fertility studies were conducted in male and female rabbits; no compound-related effects in mating and fertility indices were observed at any oral thalidomide dose level including the highest of 100 mg/kg/day to female rabbits and 500 mg/kg/day to male rabbits (approximately 5- and 25-fold the maximum human dose, respectively, based upon BSA). Testicular pathological and histopathological effects (classified as slight) were seen in male rabbits at dose levels ≥ 30

mg/kg/day (approximately 1.5-fold the maximum human dose based upon BSA).

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] 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 at 1-888-423-5436.

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. The risk to the fetus from the semen of male patients taking thalidomide is unknown.

A pre- and postnatal reproductive toxicity study was conducted in pregnant female rabbits. Compound-related increased abortion incidences and elevated fetotoxicity were observed at the lowest oral dose level of 30 mg/kg/day (approximately 1.5-fold the maximum human dose based upon BSA) and all higher dose levels. Neonatal mortality was elevated at oral dose levels to the lactating female rabbits ≥ 150 mg/kg/day (approximately 7.5-fold the maximum human dose based upon BSA). No delay in postnatal development, including learning and memory functions, were noted at the oral dose level to the lactating female rabbits of 150 mg/kg/day (average thalidomide concentrations in milk ranged from 22 to 36 µg/ml).

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

Of the total number of subjects in this clinical study of thalidomide and dexamethasone combination, 50% were 65 and over, while 15% were 75 and over. No overall differences in safety and effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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

Adverse events in Multiple Myeloma Controlled Clinical Trial

The safety analysis was conducted on 204 patients who received study drug in the randomized trial. Table 6 lists the most common treatment–emergent signs and symptoms (occurring at ≥ 10%) that were observed. The most frequently reported adverse events were constipation, sensory neuropathy, confusion, hypocalcemia, edema, dyspnea, thrombosis/embolism, and rash/desquamation (occurring in ≥20% of patients and with a frequency of ≥ 10% in patients treated with THALOMID®/dexamethasone compared with dexamethasone alone).

Twenty-three percent of patients (47/204) discontinued due to adverse events; thirty percent (31/102) from the THALOMID®/dexamethasone arm and sixteen percent (16/102) from the dexamethasone alone arm.

Table 6 Treatment-Emergent Adverse Events in ≥ 10% of All Patients Adverse Event (Safety Population; N=204)

	Thal + Dex (N=102)			Dex Alone (N=102)		
Organ System Class/Preferred Term	All Events [n,(%)]	Grade 3 Events [n,(%)]	Grade 4 Events [n,(%)]	All Events [n,(%)]	Grade 3 Events [n,(%)]	Grade 4 Events [n,(%)]
Metabolic/Laboratory	97 (95.1)	30 (29.4)	15 (14.7)	96 (94.1)	28 (27.5)	6 (5.9)

Hyperglycemia	74 (72.5)	12 (11.8)	4 (3.9)	81 (79.4)	17 (16.7)	2 (2.0)
Hypocalcemia	73 (71.6)	9 (8.8)	6 (5.9)	60 (58.8)	4 (3.9)	1 (1.0)
Hyponatremia	44 (43.1)	11 (10.8)	2 (2.0)	49 (48.0)	13 (12.7)	2 (2.0)
Hypokalemia	23 (22.5)	4 (3.9)	1 (1.0)	23 (22.5)	0 (0.0)	1 (1.0)
Hyperkalemia	19 (18.6)	1 (1.0)	2 (2.0)	20 (19.6)	2 (2.0)	0 (0.0)
Neurology	92 (90.2)	27 (26.5)	5 (4.9)	76 (74.5)	15 (14.7)	4 (3.9)
Neuropathy-sensory	55 (53.9)	3 (2.9)	1 (1.0)	28 (27.5)	1 (1.0)	0 (0.0)
Confusion	29 (28.4)	6 (5.9)	3 (2.9)	12 (11.8)	2 (2.0)	3 (2.9)
Anxiety / agitation	26 (25.5)	1 (1.0)	0 (0.0)	14 (13.7)	3 (2.9)	0 (0.0)
Tremor	26 (25.5)	1 (1.0)	0 (0.0)	6 (5.9)	0 (0.0)	0 (0.0)
Insomnia	23 (22.5)	0 (0.0)	0 (0.0)	48 (47.1)	5 (4.9)	0 (0.0)
Depression	22 (21.6)	2 (2.0)	0 (0.0)	24 (23.5)	1 (1.0)	0 (0.0)
Neuropathy-motor	22 (21.6)	7 (6.9)	1 (1.0)	16 (15.7)	5 (4.9)	1 (1.0)
Dizziness / lightheadedness	20 (19.6)	1 (1.0)	0 (0.0)	14 (13.7)	0 (0.0)	0 (0.0)
Constitutional Symptoms	91 (89.2)	17 (16.7)	3 (2.9)	84 (82.4)	15 (14.7)	2 (2.0)
Fatigue	81 (79.4)	14 (13.7)	3 (2.9)	72 (70.6)	12 (11.8)	2 (2.0)
Fever	24 (23.5)	1 (1.0)	0 (0.0)	20 (19.6)	3 (2.9)	0 (0.0)
Weight loss	23 (22.5)	1 (1.0)	0 (0.0)	21 (20.6)	2 (2.0)	0 (0.0)
Weight gain	22 (21.6)	1 (1.0)	0 (0.0)	13 (12.7)	0 (0.0)	0 (0.0)
Blood/Bone Marrow	88 (86.3)	25 (24.5)	9 (8.8)	96 (94.1)	10 (9.8)	10 (9.8)
Hemoglobin (decreased)	79 (77.5)	13 (12.7)	3 (2.9)	88 (86.3)	5 (4.9)	1 (1.0)
Leukocytes (decreased)	36 (35.3)	6 (5.9)	1 (1.0)	30 (29.4)	1 (1.0)	2 (2.0)
Neutrophils (decreased)	32 (31.4)	8 (7.8)	5 (4.9)	24 (23.5)	3 (2.9)	8 (7.8)
Platelets (decreased)	24 (23.5)	2 (2.0)	2 (2.0)	34 (33.3)	3 (2.9)	0 (0.0)
Gastrointestinal	83 (81.4)	19 (18.6)	3 (2.9)	70 (68.6)	8 (7.8)	0 (0.0)
Constipation	56 (54.9)	8 (7.8)	0 (0.0)	29 (28.4)	1 (1.0)	0 (0.0)
Anorexia	29 (28.4)	4 (3.9)	0 (0.0)	25 (24.5)	2 (2.0)	0 (0.0)
Nausea	29 (28.4)	5 (4.9)	0 (0.0)	23 (22.5)	1 (1.0)	0 (0.0)
Vomiting	12 (11.8)	2 (2.0)	0 (0.0)	12 (11.8)	1 (1.0)	0 (0.0)
Diarrhea	12 (11.8)	1 (1.0)	0 (0.0)	17 (16.7)	3 (2.9)	0 (0.0)
Dyspepsia	8 (7.8)	1 (1.0)	0 (0.0)	19 (18.6)	1 (1.0)	0 (0.0)

Cardiovascular	70 (68.6)	24 (23.5)	14 (13.7)	60 (58.8)	17 (16.7)	5 (4.9)
Edema	58 (56.9)	6 (5.9)	0 (0.0)	47 (46.1)	4 (3.9)	0 (0.0)
Thrombosis/embolism	23 (22.5)	13 (12.7)	9 (8.8)	5 (4.9)	3 (2.9)	2 (2.0)
Hypotension	16 (15.7)	7 (6.9)	2 (2.0)	15 (14.7)	2 (2.0)	3 (2.9)
Hypertension	11 (10.8)	1 (1.0)	0 (0.0)	12 (11.8)	9 (8.8)	0 (0.0)
Pain	64 (62.7)	8 (7.8)	2 (2.0)	66 (64.7)	15 (14.7)	0 (0.0)
Bone pain	31 (30.4)	3 (2.9)	2 (2.0)	37 (36.3)	11 (10.8)	0 (0.0)
Pain-other	25 (24.5)	4 (3.9)	0 (0.0)	26 (25.5)	3 (2.9)	0 (0.0)
Headache	20 (19.6)	3 (2.9)	0 (0.0)	23 (22.5)	0 (0.0)	0 (0.0)
Myalgia	17 (16.7)	0 (0.0)	0 (0.0)	14 (13.7)	1 (1.0)	0 (0.0)
Arthralgia	13 (12.7)	0 (0.0)	0 (0.0)	10 (9.8)	2 (2.0)	0 (0.0)
Pulmonary	52 (51.0)	15 (14.7)	6 (5.9)	51 (50.0)	15 (14.7)	5 (4.9)
Dyspnea	43 (42.2)	10 (9.8)	3 (2.9)	32 (31.4)	12 (11.8)	4 (3.9)
Cough	15 (14.7)	0 (0.0)	0 (0.0)	19 (18.6)	0 (0.0)	0 (0.0)
Dermatology/Skin	48 (47.1)	5 (4.9)	1 (1.0)	35 (34.3)	2 (2.0)	0 (0.0)
Rash/desquamation	31 (30.4)	4 (3.9)	0 (0.0)	18 (17.6)	2 (2.0)	0 (0.0)
Dry skin	21 (20.6)	0 (0.0)	0 (0.0)	11 (10.8)	0 (0.0)	0 (0.0)
Hepatic	47 (46.1)	5 (4.9)	2 (2.0)	45 (44.1)	3 (2.9)	1 (1.0)
Alkaline phosphatase (increased)	27 (26.5)	0 (0.0)	0 (0.0)	29 (28.4)	1 (1.0)	0 (0.0)
SGOT (increased)	25 (24.5)	1 (1.0)	1 (1.0)	24 (23.5)	1 (1.0)	1 (1.0)
Bilirubin (increased)	14 (13.7)	1 (1.0)	1 (1.0)	10 (9.8)	1 (1.0)	1 (1.0)
Renal/Genitourinary	43 (42.2)	3 (2.9)	3 (2.9)	49 (48.0)	4 (3.9)	3 (2.9)
Creatinine	36 (35.3)	1 (1.0)	1 (1.0)	43 (42.2)	2 (2.0)	2 (2.0)
Musculoskeletal	42 (41.2)	8 (7.8)	2 (2.0)	41 (40.2)	11 (10.8)	3 (2.9)
Muscle weakness	41 (40.2)	6 (5.9)	1 (1.0)	38 (37.3)	10 (9.8)	3 (2.9)
Infection/Febrile Neutropenia	23 (22.5)	5 (4.9)	2 (2.0)	28 (27.5)	6 (5.9)	6 (5.9)
Infection without neutropenia	19 (17.6)	4 (3.9)	1 (1.0)	18 (17.6)	4 (3.9)	2 (2.0)

Incidence in ENL Controlled Clinical Trials

Table 7 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 7 also lists treatment-emergent adverse events that occurred in at least 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 7 Summary of Adverse Events (AEs) Reported in Celgene-sponsored Controlled Clinical Trials

Body System/Adverse Event	All AEs Reported in ENL Patients	AEs Reported in ≥3 HIV-seropositive Patients		
		Thalidomide		Placebo
	50 to 300 mg/day (N=24)	100 mg/day (N=36)	200 mg/day (N=32)	(N=35)
Body as a Whole	**16 (66.7%)**	**18 (50.0%)**	**19 (59.4%)**	**13 (37.1%)**
Abdominal pain	1 (4.2%)	1 (2.8%)	1 (3.1%)	4 (11.4%)
Accidental injury	1 (4.2%)	2 (5.6%)	0	1 (2.9%)
Asthenia	2 (8.3%)	2 (5.6%)	7 (21.9%)	1 (2.9%)
Back pain	1 (4.2%)	2 (5.6%)	0	0
Chills	1 (4.2%)	0	3 (9.4%)	4 (11.4%)
Facial edema	1 (4.2%)	0	0	0
Fever	0	7 (19.4%)	7 (21.9%)	6 (17.1%)
Headache	3 (12.5%)	6 (16.7%)	6 (18.7%)	4 (11.4%)
Infection	0	3 (8.3%)	2 (6.3%)	1 (2.9%)
Malaise	2 (8.3%)	0	0	0
Neck pain	1 (4.2%)	0	0	0
Neck rigidity	1 (4.2%)	0	0	0
Pain	2 (8.3%)	0	1 (3.1%)	2 (5.7%)
Digestive System	**5 (20.8%)**	**16 (44.4%)**	**16 (50.0%)**	**15 (42.9%)**
Anorexia	0	1 (2.8%)	3 (9.4%)	2 (5.7%)
Constipation	1 (4.2%)	1 (2.8%)	3 (9.4%)	0
Diarrhea	1 (4.2%)	4 (11.1%)	6 (18.7%)	6 (17.1%)
Dry mouth	0	3 (8.3%)	3 (9.4%)	2 (5.7%)
Flatulence	0	3 (8.3%)	0	2 (5.7%)
Liver function tests multiple abnormalities	0	0	3 (9.4%)	0
Nausea	1 (4.2%)	0	4 (12.5%)	1 (2.9%)
Oral moniliasis	1 (4.2%)	4 (11.1%)	2 (6.3%)	0
Tooth pain	1 (4.2%)	0	0	0
Hemic and Lymphatic	**0**	**8 (22.2%)**	**13 (40.6%)**	**10 (28.6%)**
Anemia	0	2 (5.6%)	4 (12.5%)	3 (8.6%)
Leukopenia	0	6 (16.7%)	8 (25.0%)	3 (8.6%)
Lymphadenopathy	0	2 (5.6%)	4 (12.5%)	3 (8.6%)
Metabolic and Endocrine Disorders	**1 (4.2%)**	**8 (22.2%)**	**12 (37.5%)**	**8 (22.9%)**
Edema peripheral	1 (4.2%)	3 (8.3%)	1 (3.1%)	0
Hyperlipemia	0	2 (5.6%)	3 (9.4%)	1 (2.9%)
SGOT increased	0	1 (2.8%)	4 (12.5%)	2 (5.7%)
Nervous System	**13 (54.2%)**	**19 (52.8%)**	**18 (56.3%)**	**12 (34.3%)**
Agitation	0	0	3 (9.4%)	0
Dizziness	1 (4.2%)	7 (19.4%)	6 (18.7%)	0
Insomnia	0	0	3 (9.4%)	2 (5.7%)
Nervousness	0	1 (2.8%)	3 (9.4%)	0
Neuropathy	0	3 (8.3%)	0	0

Paresthesia	0	2 (5.6%)	5 (15.6%)	4 (11.4%)
Somnolence	9 (37.5%)	13 (36.1%)	12 (37.5%)	4 (11.4%)
Tremor	1 (4.2%)	0	0	0
Vertigo	2 (8.3%)	0	0	0
Respiratory System	**3 (12.5%)**	**9 (25.0%)**	**6 (18.7%)**	**9 (25.7%)**
Pharyngitis	1 (4.2%)	3 (8.3%)	2 (6.3%)	2 (5.7%)
Rhinitis	1 (4.2%)	0	0	4 (11.4%)
Sinusitis	1 (4.2%)	3 (8.3%)	1 (3.1%)	2 (5.7%)
Skin and Appendages	**10 (41.7%)**	**17 (47.2%)**	**18 (56.3%)**	**19 (54.3%)**
Acne	0	4 (11.1%)	1 (3.1%)	0
Dermatitis fungal	1 (4.2%)	2 (5.6%)	3 (9.4%)	0
Nail disorder	1 (4.2%)	0	1 (3.1%)	0
Pruritus	2 (8.3%)	1 (2.8%)	2 (6.3%)	2 (5.7%)
Rash	5 (20.8%)	9 (25.0%)	8 (25.0%)	11 (31.4%)
Rash maculo-papular	1 (4.2%)	6 (16.7%)	6 (18.7%)	2 (5.7%)
Sweating	0	0	4 (12.5%)	4 (11.4%)
Urogenital System	**2 (8.3%)**	**6 (16.7%)**	**2 (6.3%)**	**4 (11.4%)**
Albuminuria	0	3 (8.3%)	1 (3.1%)	2 (5.7%)
Hematuria	0	4 (11.1%)	0	1 (2.9%)
Impotence	2 (8.3%)	1 (2.8%)	0	0

Other Adverse Events Observed in ENL Patients

Thalidomide in doses up to 400 mg/day has been administered investigationally in the United States over a 19-year period in 1465 patients with ENL. The published literature describes the treatment of an additional 1678 patients. To provide a meaningful estimate of the proportion of the individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using a modified COSTART dictionary/terminology. These categories are used in the listing below. All reported events are included except those already listed in the previous table. Due to the fact that these data were collected from uncontrolled studies, the incidence rate cannot be determined. As mentioned previously, **no causal relationship between thalidomide and these events can be conclusively determined at this time.** These are reports of all adverse events noted by investigators in patients to whom they had administered thalidomide.

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

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

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, thyroid 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 Observed in Post-Marketing Use

Cardiovascular System: Cardiac arrhythmias including atrial fibrillation, bradycardia, tachycardia, sick sinus syndrome and EKG abnormalities.

Digestive System: Intestinal perforation.

Metabolic and Endocrine: Electrolyte imbalance including hypercalcemia or hypocalcemia, hyperkalemia and hypokalemia, hyponatremia, hypothyroidism, and increased alkaline phosphatase, tumor lysis syndrome.

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.

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.

Multiple Myeloma

THALOMID® (thalidomide) is administered in combination with dexamethasone in 28-day treatment cycles. The dose of THALOMID® is 200 mg administered orally once daily with water, preferably at bedtime and at least 1-hour after the evening meal. The dose of dexamethasone is 40 mg daily administered orally on days 1-4, 9-12, and 17-20 every 28 days.

Patients who develop side effects such as constipation, oversedation, or peripheral neuropathy may benefit by either temporarily discontinuing the drug or continuing at a lower dose. With the abatement of these side effects, the drug may be started at a lower dose or at the previous dose based on clinical judgment.

Erythema Nodosum Leprosum

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) Capsules are supplied in the following dosages:

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

Individual blister packs of 28 capsules (NDC 59572-205-14).

Boxes of 280 containing 10 prescription packs of 28 capsules each (NDC 59572-205-94).

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

Individual blister packs of 28 capsules (NDC 59572-210-15).

Boxes of 140 containing 5 prescription packs of 28 capsules each (NDC 59572-210-95).

150 mg capsules [tan and blue], imprinted "Celgene/ 150 mg" with a "Do Not Get Pregnant" logo.

Individual blister packs of 28 capsules (NDC 59572-215-13).

Boxes of 112 containing 4 prescription packs of 28 capsules (NDC 59572-215-93).

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

Individual blister packs of 28 capsules (NDC 59572-220-16).

Boxes of 84 containing 3 prescription packs of 28 capsules each (NDC 59572-220-96).

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 1-888-423-5436 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. A NEW PRESCRIPTION IS REQUIRED FOR FURTHER DISPENSING. 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 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

86 Morris Avenue

Summit, New Jersey 07901

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] 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 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
Partner's vasectomy

Cervical cap

- These birth control methods must be used for at least 4 weeks before beginning THALOMID® (thalidomide) therapy, during THALOMID® (thalidomide) therapy, and for 4 weeks following discontinuation of THALOMID® (thalidomide) therapy.

- 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).

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THALPI.01X XX/06 CG

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20785	SUPPL-39	CELGENE CORP	THALOMID (THALIDOMIDE) 50MG CAPSULES

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/s/

ROBERT L JUSTICE
08/03/2010