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THALOMID[®] (thalidomide)

NDA # 020785

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

1. GOALS

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

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

2. REMS ELEMENTS

2.1. Elements to Assure Safe Use

2.1.1. Healthcare providers who prescribe THALOMID are specially certified.

Celgene will ensure that healthcare providers who prescribe THALOMID are specially certified in the THALOMID REMS[®] program. THALOMID[®] (thalidomide) is available only through a restricted distribution program, THALOMID REMS[®].

To become certified, each prescriber must complete the Prescriber Enrollment Form and agree to do the following:

- a. Provide patient counseling on the benefits and risks of THALOMID therapy, including risks described in the BOXED WARNINGS.
- b. Enroll each patient by completing and submitting to the Celgene Customer Care Center via mail (86 Morris Avenue, Summit, NJ 07901), email (customer care@celgene.com), fax (1-888-432-9325), or online (www.celgeneriskmanagement.com), a signed Patient-Physician Agreement Form (PPAF) 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 THALOMID REMS[®] 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 reproductive 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 (1-888-423-5436)).
- f. Complete a prescriber survey (phone or online) for every patient (new and follow-up), obtain a unique prescription authorization number for each prescription written, and include this authorization number on the prescription. The authorization number can be obtained by contacting the Celgene Customer Care Center, using the automated IVR system, or via the www.CelgeneRiskManagement.com website.
 - o For females of reproductive potential, authorization numbers are valid only for 7 days from date of last pregnancy test.
 - o Authorization numbers are valid for 30 days from the date it is issued for all other patients.
- g. Facilitate compliance with the mandatory THALOMID REMS® patient survey by instructing patients to complete the mandatory surveys (phone or online) at program specified frequencies.
- h. Prescribe no more than a 4-week (28-day) supply, with no automatic refills or telephone prescriptions.
- i. Contact a pharmacy certified by the THALOMID REMS® program to fill the THALOMID prescription.
- j. Return all unused THALOMID brought in by patients to Celgene Customer Care.
- k. Re-enroll patients in the THALOMID REMS® program if THALOMID is required and previous therapy with THALOMID has been discontinued for 12 consecutive months.

Celgene will:

1. Ensure that the THALOMID REMS® program materials including prescriber enrollment are available on the CelgeneRiskManagement.com website or can be obtained by contacting Celgene Customer Care Center at 1-888-423-5436
2. Maintain a secure database of all THALOMID REMS® certified prescribers.
3. Monitor to ensure that only THALOMID REMS® certified prescribers are prescribing THALOMID.
4. 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 enrollment process:
 - a. **Adult female of reproductive potential:** all females who are menstruating, amenorrheic from previous medical treatments, under 50 years, and/or perimenopausal.
 - b. **Female child of reproductive potential:** all females under 18 years who are menstruating.
 - c. **Adult female NOT of reproductive potential:** females who have had a natural menopause for at least 24 consecutive months, a hysterectomy, and/or bilateral oophorectomy.

- d. **Female child NOT of reproductive potential:** all females under 18 years who are not menstruating.
 - e. **Adult males 18 years or older**
 - f. **Male child under 18 years**
5. Monitor certified prescriber compliance with the THALOMID REMS[®] program, including patient risk categorization and the appropriate corresponding counseling requirements, contraception requirements, pregnancy testing, and survey completion for all patients treated with THALOMID.
 6. Institute corrective action and prevent the certified prescriber from prescribing THALOMID if the prescriber is found to be non-compliant with the THALOMID REMS[®] program.
 7. Train THALOMID REMS[®] program certified prescribers in adverse experience reporting procedures, including the requirement to immediately report to Celgene any suspected embryo-fetal exposure to THALOMID if a pregnancy occurs.
 8. Ensure that once the prescriber submits the completed PPAF, the prescriber will receive a confirmation letter via fax or online to confirm the patient's enrollment and signify that the prescriber and patient surveys can be taken to receive an authorization number for the THALOMID prescription (for all males, the PPAF is considered the initial survey). The authorization number is written on the THALOMID prescription.
 9. Ensure that, for subsequent prescriptions, the prescriber completes a telephone or online 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 survey will allow the prescriber to obtain a new authorization number every time a prescription for THALOMID is written.

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

- [Prescriber Enrollment Form](#)
- [Patient Prescription Form](#)
- [Patient Prescription Form \(Veterans Health Administration\)](#)
- [Prescriber Guide to THALOMID REMS[®] Program](#)
- [THALOMID REMS[®] At-A-Glance](#)
- [Welcome Letter](#)
- [Celgene Risk Management.com website](#)

2.1.2. THALOMID will only be dispensed by pharmacies that are specially certified.

Celgene will ensure that THALOMID is only dispensed from THALOMID REMS[®] program certified pharmacies. To become a THALOMID REMS[®] program certified pharmacy, the pharmacy must agree to do the following before filling a THALOMID prescription:

- a. Only accept prescriptions with a prescription authorization number. Authorization numbers are valid for 7 days from date of last pregnancy test for females of reproductive potential and 30 days from the date it is issued for all other patients.
- b. Dispense no more than a 4-week (28-day) supply, and require a new prescription from the patient prior to dispensing additional THALOMID.

- c. Dispense subsequent prescriptions only if there are 7 days or less remaining on an existing THALOMID prescription.
- d. Obtain a THALOMID REMS[®] confirmation number from the Celgene Customer Care Center (phone or online) and write this confirmation number on the prescription. The THALOMID REMS[®] confirmation number may be obtained using the following procedure:
 - 1. Enter the pharmacy identification number (NABP or DEA);
 - 2. Enter the prescription authorization number written on the prescription;
 - 3. Enter the number of capsules and milligram (mg) strength being dispensed;
 - 4. Dispense or ship the prescribed THALOMID within 24 hours of obtaining and recording the THALOMID REMS[®] confirmation number and confirmation date.
- e. Dispense THALOMID only after a THALOMID REMS[®] confirmation number is obtained. If no confirmation is obtained, then no THALOMID is dispensed. Contact the patient's physician and Celgene for further instruction.
- f. Accept unused THALOMID (previously dispensed) from a patient or patient caregiver and return to Celgene Corporation for proper disposal.
- g. For each patient receiving treatment, retain a record of each THALOMID prescription dispensed and the corresponding completed Education and Counseling Checklist.
- h. Complete the checklist that applies to the patient risk category written on the front of the Education and Counseling Checklist for Pharmacies.
- i. Provide counseling to patients and/or guardians of patients under 18 years of age receiving THALOMID treatment.
 - a. Counsel all patients and guardians of patients under 18 years of age on the following:
 - 1. The benefits and risks of THALOMID therapy.
 - 2. Not sharing THALOMID medication.
 - 3. Not donating blood while taking THALOMID, during dose interruptions, and for 4 weeks after stopping THALOMID.
 - 4. Not to break, chew, or open THALOMID capsules.
 - 5. Instructions on THALOMID dose and administration.
 - 6. To read the THALOMID REMS[®] program education materials and encourage compliance with the requirements.
 - b. In addition to above, counsel **Females of Reproductive Potential** on the following:
 - 1. The potential for embryo-fetal toxicity with exposure to THALOMID.
 - 2. Using 2 methods of effective birth control (at least one highly effective method and one effective method) at the same time or abstaining from heterosexual sexual intercourse.
 - 3. Continuing to use 2 methods of effective of birth control (at least one highly effective method and one effective method) at the same time if THALOMID therapy is interrupted and for at least 4 weeks after therapy is discontinued.
 - 4. Obtaining a pregnancy test weekly during the first 4 weeks of THALOMID use, then a repeat pregnancy test every 4 weeks in females with regular menstrual cycles, and every 2 weeks in females with irregular menstrual cycles.
 - 5. The need to stop taking THALOMID and notify their THALOMID prescriber immediately if they become pregnant or suspect they may be pregnant.

- c. In addition to items listed for all patients above, counsel **Males** receiving THALOMID treatment about the potential for embryo-fetal toxicity with exposure to THALOMID and the importance of using barrier contraception by wearing a latex or synthetic condom when engaging in sexual intercourse with a female of reproductive potential even if the male receiving THALOMID has had a successful vasectomy.
 1. The need to not donate sperm while taking THALOMID, during dose interruptions, and for 4 weeks after stopping THALOMID.
- d. Counsel the **Parent or legal guardian of Female Child NOT of reproductive potential** who is receiving THALOMID treatment about the need to inform their THALOMID prescriber when the child begins menses.

Before a certified pharmacy dispenses THALOMID, Celgene will train the appropriate pharmacy staff:

- a. About the THALOMID REMS[®] program
 - b. About the procedures for reporting adverse experiences to Celgene, including the requirement to immediately report to Celgene any suspected embryo-fetal exposure to THALOMID if a pregnancy occurs.
1. The following materials are part of the REMS and are appended:
 - [Pharmacy Guide to the THALOMID REMS[®] Program](#)
 - [Education and Counseling Checklist for Pharmacies](#)
 - [Celgene REMS Programs Pharmacy Training: the THALOMID REMS[®] Program](#)
 - [Pharmacy Certification Quiz \(the THALOMID REMS[®] Program\)](#)

2.1.3. Celgene will ensure that THALOMID will only be dispensed to patients enrolled in the THALOMID REMS[®] program with evidence or other documentation of safe-use conditions.

Celgene will ensure that all patients treated with THALOMID are enrolled by a certified prescriber. The prescriber will enroll the patient by completing Patient-Physician Agreement Form and submitting the form via mail (86 Morris Avenue, Summit, NJ 07901), fax (1-888-432-9325), email (customer care@celgene.com) or online (www.celgeneriskmanagement.com) for each patient who receives THALOMID. Each patient and/or guardian of patients under 18 years of age 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, including dose interruptions, and for 4 weeks after stopping THALOMID;

- v. they might be asked to participate in the THALOMID Pregnancy Exposure Registry; and
 - vi. they may be contacted by Celgene about following the rules of the REMS.
- b. In addition, each patient and/or guardian of patients under 18 years of age consents to participate in the program by:
- i. agreeing to return unused THALOMID to Celgene or their THALOMID prescriber, or to the pharmacy that dispensed the THALOMID to them;
 - ii. agreeing to participate in a monthly (telephone or online) survey while on THALOMID (with the exception of Adult Females Not of Reproductive Potential who are required to take a survey once every six months); and
 - iii. reviewing the THALOMID REMS® program educational materials and asking their prescriber any questions that have not been answered.

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

Females of Reproductive Potential and guardians of Female Children of Reproductive Potential 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 at least 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 within 10 to 14 days and 24 hours prior to starting THALOMID, every week for at least the first 4 weeks of THALOMID therapy, and then every 4 weeks if the Female of Reproductive Potential has regular menstrual cycles, or every 2 weeks if the Female of Reproductive Potential has irregular menstrual cycles, while receiving THALOMID;
- e. will immediately stop taking THALOMID 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 Female of Reproductive Potential or guardian of a Female Child of Reproductive Potential can call the Celgene Customer Care Center at 1-888-423-5436.

Males or guardians of Males will attest that they/their child will:

- a. never have unprotected sexual contact with a female who can become pregnant;
- b. wear a latex or synthetic condom every time the male patient has sexual contact with a female who is or who can become pregnant; continue condom use with sexual contact while the male patient is receiving THALOMID treatment, during dose interruptions, and for 4 weeks after the male patient stops taking THALOMID, even if the patient has had a successful vasectomy; and
- c. inform their certified prescriber if the male patient has unprotected sexual contact with a female who can become pregnant, or if they think for any reason that the male patient's sexual partner might be pregnant; if the prescriber is not available, the male patient or

- guardian of an underage male patient can call the Celgene Customer Care Center at 1-888-423-5436;
- d. not donate sperm while taking (including dose interruptions) and for 4 weeks after stopping THALOMID.

The following appended materials are part of the REMS:

- [Patient-Physician Agreement Form for Adult Male](#)
- [Patient-Physician Agreement Form for Male Child](#)
- [Patient-Physician Agreement Form Adult Female Who Can Not Get Pregnant](#)
- [Patient-Physician Agreement Form Adult Female Who Can Get Pregnant](#)
- [Patient-Physician Agreement Form Female Child Who Can Not Get Pregnant](#)
- [Patient-Physician Agreement Form Female Child Who Can Get Pregnant](#)
- [Patient Guide to THALOMID REMS® Program](#)
- [Emergency Contraception Brochure](#)
- [Patient Survey Reminder Card](#)
- [THALOMID Risk Evaluation and Mitigation Strategy \(REMS\) Program Education and Prescribing Safety Kit](#)
- [THALOMID REMS® Patient Resource Pack Envelope](#)

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

Upon receiving a report of pregnancy from the THALOMID REMS® program, Celgene Pregnancy Prevention Plan programs in the rest of the world, clinical trials, or directly from a prescriber, a pharmacy, or a 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 (should one occur) in female patients of reproductive potential and female partners of male patients who are exposed to THALOMID and to understand the root cause of the pregnancy.

2.2. Implementation System

The implementation system will include the following:

- 1) Celgene will maintain a secure database of all certified entities, including enrolled patients and certified prescribers and pharmacies to monitor and evaluate implementation of the elements provided for in Sections [2.1.1](#), [2.1.2](#), and [2.1.3](#).
- 2) Celgene will monitor THALOMID REMS® program pharmacy certification 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 THALOMID REMS[®] program, Celgene will institute corrective action and may de-activate pharmacies for which re-training has proven ineffective, removing them from the THALOMID REMS[®] program.
 - b. Celgene will perform regular audits of contract pharmacies participating in the THALOMID REMS[®] program. For pharmacies that have been in the program for more than two years, Celgene will perform a risk-based assessment to select which pharmacies will be audited. The THALOMID REMS[®] program compliance audits will be performed by internal auditors of Celgene and/or outside auditors contracted and trained by Celgene.
- 3) Celgene will monitor and ensure that the prescriptions are filled within the allowed timeframes.
 - 4) Celgene Customer Care Center will address customer complaints received that are related to the THALOMID REMS[®] program and distribution and dispensing of THALOMID.
 - 5) 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 THALOMID Pregnancy Exposure Registry and to understand the root cause of the pregnancy.
 - 6) 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.
 - 7) Celgene will develop and follow written procedures related to the implementation of the REMS.

2.3. Timetable for Submission of Assessment Reports

Celgene will submit REMS assessments every two years beginning with submission of the next assessment by August 3, 2016. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should 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.