A. THALOMID REMS Program

I. Administrative Information
Application Number: NDA 020785
Application Holder: Celgene Corporation
Initial REMS Approval: 08/2010
Most Recent REMS Update: 07/2021

II. REMS Goals
The goals of the THALOMID REMS® are as follows:
1. To prevent the risk of embryo-fetal exposure to THALOMID®.
2. To inform prescribers, patients, and pharmacists on the serious risks and safe-use conditions for THALOMID.

III. REMS Requirements
Celgene must ensure that healthcare providers, patients, and pharmacies comply with the following requirements:

1. Healthcare providers who prescribe THALOMID must:
   1. Review the drug’s Prescribing Information.
   2. Enroll in the REMS by completing, the Prescriber Enrollment Form and submitting it to the REMS Program.

   Before treatment initiation (first prescription); within 10-14 days and again within 24 hours
   4. For females (adults and children) who can get pregnant: Assess the patient’s pregnancy status by ordering and confirming a negative pregnancy test result. Document and submit the result to the REMS Program.

   Before treatment initiation (first prescription)
   5. For all patients: Counsel the patient on the benefits and risks of THALOMID therapy, including risks described in the Boxed WARNINGS and the need to complete mandatory patient surveys using the Patient Guide and Patient-
Physician Agreement Form (PPAF). Provide a copy of the materials to the patient.

6. For females (adults and children) who can get pregnant: Counsel the patient on contraception requirements and emergency contraception using the Patient Guide and the Emergency Contraception Brochure. Provide a copy of the materials to the patient.

7. For males (adults and children): Counsel the patient on the barrier contraception requirements and emergency contraception using the Patient Guide and the Emergency Contraception Brochure. Provide a copy of the materials to the patient.

8. Enroll the patient by completing and submitting the Agreement Form for Female Child Who Can Get Pregnant, Agreement Form for Female Child Who Can Not Get Pregnant, Agreement Form for Male Child, Agreement Form for Adult Female Who Can Get Pregnant, Agreement Form for Adult Female Who Can Not Get Pregnant, or Agreement Form for Adult Male to the REMS Program.

9. Obtain authorization by contacting the REMS Program to complete the prescriber survey to verify the patient’s reproductive status, negative pregnancy test status, and completion of counseling. Document the prescription authorization number and the patient’s risk category on the prescription.

10. Prescribe no more than a 28 days’ supply.

11. Not prescribe refills or prescribe over the phone.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Task</th>
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</thead>
<tbody>
<tr>
<td>During treatment; weekly for at least the first 4 weeks</td>
<td>12. For females (adults and children) who can get pregnant: Assess the patient’s pregnancy status by ordering and reviewing the results of her pregnancy test.</td>
</tr>
<tr>
<td>During treatment; every 2 weeks after the first 4 weeks</td>
<td>13. For females (adults and children) with irregular menstrual cycles who can get pregnant: Assess the patient’s pregnancy status by ordering and reviewing the results of her pregnancy test.</td>
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<tr>
<td>During treatment; every 4 weeks after the first 4 weeks</td>
<td>14. For females (adults and children) with regular menstrual cycles who can get pregnant: Assess the patient’s pregnancy status by ordering and reviewing the results of her pregnancy test. Document and submit the results to the REMS Program.</td>
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<tr>
<td>During treatment: before each prescription</td>
<td>15. For all patients: Counsel the patient on the need to complete the patient survey.</td>
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<tr>
<td></td>
<td>16. For females (adults and children) who can get pregnant: Counsel the patient on using contraception requirements and emergency contraception using the Patient Guide and the Emergency Contraception Brochure.</td>
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<td></td>
<td>17. For males (adults and children): Counsel the patient on the barrier contraception requirements using the Patient Guide.</td>
</tr>
</tbody>
</table>
18. Obtain authorization by contacting the REMS Program to complete the prescriber survey to verify the patient’s reproductive status, negative pregnancy test status, and completion of counseling. Document the prescription authorization number and the patient’s risk category on the prescription.

19. Prescribe no more than a 28 days’ supply.

20. Not prescribe refills or prescribe over the phone.

21. Report any pregnancies in female patients or female partners of male patients immediately to the REMS Program.

22. Return all unused product from patients to Celgene.

## 2. Females (adults and children) who can get pregnant who are prescribed THALOMID:

<table>
<thead>
<tr>
<th>Before treatment initiation; 4 weeks</th>
<th>1. Adhere to the safe use conditions: using contraception and not getting pregnant as described in the Patient Guide and the Patient-Physician Agreement Form.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment initiation; within 10-14 days and again within 24 hours</td>
<td>2. Get a pregnancy test as directed by your prescriber.</td>
</tr>
<tr>
<td>Before treatment initiation</td>
<td>3. Receive counseling from the prescriber on the benefits and risks of THALOMID therapy and the need to complete the patient survey, on contraception requirements and emergency contraception.</td>
</tr>
<tr>
<td></td>
<td>5. Enroll into the REMS Program by completing the Patient-Physician Agreement Form for Adult Females Who Can Get Pregnant or Patient-Physician Agreement Form for Female Child Who Can Get Pregnant with the prescriber. Enrollment information will be provided to the REMS Program.</td>
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<td></td>
<td>6. Complete the patient survey.</td>
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<tr>
<td></td>
<td>7. Receive counseling from the pharmacy on the benefits and risks of THALOMID; not sharing THALOMID; not donating blood; not to breaking, chewing, or opening THALOMID capsules; instructions on dose and administration; reading the THALOMID REMS education materials; and being compliant with the REMS requirements.</td>
</tr>
<tr>
<td></td>
<td>8. Receive counseling from the pharmacy on the embryo-fetal toxicity with exposure to THALOMID; contraception requirements; pregnancy testing requirement; not taking THALOMID if pregnant, breastfeeding, or not using contraception; and to immediately stop taking THALOMID and notify the prescriber if pregnant or suspect they may be pregnant.</td>
</tr>
<tr>
<td>During treatment; weekly at least the first 4 weeks</td>
<td>9. Get a pregnancy test as directed by your prescriber.</td>
</tr>
</tbody>
</table>
During treatment; before each prescription

10. Receive counseling from the prescriber on contraception requirements and emergency contraception and the need to complete the patient survey.

11. Get a pregnancy test as directed by your prescriber.

12. Receive counseling from the pharmacy on the benefits and risks of THALOMID; not sharing THALOMID; not donating blood; not to breaking, chewing, or opening THALOMID capsules; instructions on dose and administration; reading the THALOMID REMS education materials; and being compliant with the REMS requirements.

13. Receive counseling from the pharmacy on embryo-fetal toxicity with exposure to THALOMID; contraception requirements; pregnancy testing requirement; not taking THALOMID if pregnant, breastfeeding or not using contraception; and to immediately stop taking THALOMID and notify the prescriber if pregnant or suspect they may be pregnant.


During treatment and after treatment discontinuation; for 4 weeks

15. Adhere to the safe-use conditions: Not donating blood.

16. Adhere to the safe-use conditions: Using contraception as described in the Patient Guide and the Patient-Physician Agreement Form; not taking THALOMID if pregnant, breastfeeding, or not using contraception; and not getting pregnant.

At all times

17. Inform the prescriber if pregnant, miss a menstrual period, experiences unusual menstrual bleeding, stops using contraception, or think for any reason that you may be pregnant. Stop taking THALOMID immediately.

18. Return unused THALOMID to Celgene, your prescriber, or the pharmacy that dispensed their THALOMID.

19. Adhere to safe-use conditions: Not sharing THALOMID; not breaking, chewing, or opening THALOMID capsules; and keeping THALOMID out of reach of children.

3. Adult females who cannot get pregnant who are prescribed THALOMID:

Before treatment initiation

1. Receive counseling from the prescriber on the benefits and risks of THALOMID and the need to complete the patient survey.

2. Review the Patient Guide.

3. Complete the patient survey.

4. Enroll into the REMS Program by completing the Patient-Physician Agreement Form for Adult Female Who Can Not Get Pregnant with the prescriber. Enrollment information will be provided to the REMS Program.

5. Receive counseling from the pharmacy on the benefits and risks of THALOMID therapy; not sharing THALOMID; not donating blood; not to breaking, chewing, or opening THALOMID capsules; instructions on dose and...
<table>
<thead>
<tr>
<th>Activity</th>
<th>Instructions</th>
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<tbody>
<tr>
<td><strong>During treatment; before each prescription</strong></td>
<td>6. Receive counseling from the pharmacy on the benefits and risks of THALOMID therapy; not sharing THALOMID; not donating blood; not to breaking, chewing, or opening THALOMID capsules; instructions on dose and administration; reading the THALOMID REMS education materials; and being compliant with the REMS requirements.</td>
</tr>
</tbody>
</table>
| **During treatment; every 6 months** | 7. Receive counseling from the prescriber on the need to complete the patient survey.  
8. Complete the patient survey. |
| **During treatment and after treatment discontinuation; for 4 weeks** | 9. Adhere to the safe-use conditions: Not donating blood. |
| **At all times** | 10. Return unused THALOMID to Celgene, the prescriber, or the pharmacy that dispensed their THALOMID.  
11. Adhere to the safe-use conditions: Not sharing THALOMID; not breaking, chewing, or opening THALOMID capsules; and keeping THALOMID out of reach of children. |

**4. Female children who cannot get pregnant who are prescribed THALOMID:**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Instructions</th>
</tr>
</thead>
</table>
| **Before treatment initiation** | 1. Receive counseling from the prescriber on the benefits and risks of THALOMID from the prescriber and the need to complete the patient survey.  
2. Review the Patient Guide.  
3. Enroll into the REMS Program by completing a Patient-Physician Agreement Form for Female Child Who Can Not Get Pregnant with the prescriber. Enrollment information will be provided to the REMS Program.  
4. Complete the patient survey.  
5. Receive counseling from the pharmacy on the benefits and risks of THALOMID; not sharing THALOMID; not donating blood; not breaking, chewing, or opening THALOMID capsules; instructions on dose and administration; reading the THALOMID REMS education materials; and being compliant with the REMS requirements.  
6. Receive counseling from the pharmacy on informing your THALOMID prescriber when the patient begins menses. |
| **During treatment; before each prescription** | 7. Receive counseling from the prescriber on the need to complete the patient survey.  
8. Receive counseling from the pharmacy on the benefits and risks of THALOMID; not sharing THALOMID; not donating blood; not breaking, chewing, or opening THALOMID capsules; instructions on dose and administration; reading... |
9. Receive counseling from the pharmacy to inform your THALOMID prescriber when the patient begins menses.

10. Complete the patient survey.

During treatment and after treatment discontinuation; for 4 weeks

11. Adhere to the safe-use conditions: not donating blood.

At all times

12. Inform the prescriber when the patient begins menses.

13. Return unused THALOMID to the Celgene, your prescriber, or the pharmacy that dispensed their THALOMID.

14. Adhere to the safe-use conditions: Not sharing THALOMID; not breaking, chewing, or opening THALOMID capsules; and keeping THALOMID out of reach of children.

5. Males (adults and children) who are prescribed THALOMID:

Before treatment initiation

1. Receive counseling from the prescriber on the benefits and risks of THALOMID, the need to complete the patient survey, barrier contraception requirements, and emergency contraception.


3. Enroll into the REMS Program by completing a Patient-Physician Agreement Form for Adult Male or Patient-Physician Agreement Form for Male Child with the prescriber. Enrollment information will be provided to the REMS Program.

4. Receive counseling from the pharmacy on the benefits and risks of THALOMID; not sharing THALOMID; not donating blood; not breaking, chewing, or opening THALOMID capsules; instructions on dose and administration; reading the THALOMID REMS education materials; and being compliant with the REMS requirements.

5. Receive counseling from the pharmacy on embryo-fetal toxicity with exposure to THALOMID; barrier contraception requirements; and not donating sperm.

During treatment; before each prescription

6. Receive counseling from the prescriber on barrier contraception requirements and emergency contraception, and the need to complete the patient survey.

7. Receive counseling from the pharmacy on the benefits and risks of THALOMID; not sharing THALOMID; not donating blood; not breaking, chewing, or opening THALOMID capsules; instructions on dose and administration; reading the THALOMID REMS education materials; and being compliant with the REMS requirements.
8. Receive counseling from the pharmacy on embryo-fetal toxicity with exposure to THALOMID; barrier contraception requirements; and not donating sperm.

9. Complete the patient survey.

During treatment and after treatment discontinuation; for 4 weeks

10. Adhere to the safe-use conditions: Using barrier contraception as described in the Patient Guide and Patient-Physician Agreement Form.

11. Adhere to the safe-use conditions: Not donating sperm.

At all times

12. Inform the prescriber about unprotected sexual contact with a female who can become pregnant, or about a sexual partner who might be pregnant.

13. Return unused THALOMID to Celgene, your prescriber, or the pharmacy that dispensed their THALOMID.

14. Adhere to safe-use conditions: Not sharing THALOMID; not breaking, chewing, or opening THALOMID capsules; and keeping THALOMID out of reach of children.

6. Pharmacies that dispense THALOMID must:

To become certified to dispense

1. Review the following: Pharmacy Guide, REMS Program Pharmacy Training, Pharmacy Certification Quiz.

2. Establish processes and procedures to verify there are 7 days or less remaining on the patient’s existing prescription, no more than 28 days’ supply is dispensed, and the prescriber provided the authorization number and patient risk category on the prescription.

Before dispensing

3. For all patients: Counsel the patient on the benefits and risks of THALOMID, and safe-use conditions using the Education and Counseling Checklist for Pharmacies.

4. For females (adult and children) who can get pregnant, counsel on the embryo-fetal toxicity with exposure to THALOMID and her safe-use conditions using the Education and Counseling Checklist for Pharmacies.

5. For female children who cannot get pregnant: Counsel the patient to inform the prescriber when menses begins using the Education and Counseling Checklist for Pharmacies.

6. For males (adult and children): Counsel the patient on the embryo-fetal toxicity with exposure to THALOMID and additional safe-use conditions using the Education and Counseling Checklist for Pharmacies.

7. Verify that a prescription authorization number and patient risk category is documented on each prescription through the processes and procedures established as a requirement of the REMS Program.

8. Obtain confirmation number to dispense each prescription by contacting the REMS Program to verify the prescriber is
certified, the patient is enrolled and is not pregnant, and the authorization number is valid.

9. Document the confirmation number and date it was obtained on the prescription.


11. Dispense no more than a 28 days’ supply.

12. Dispense only if there are 7 days or less remaining on the existing prescription.

13. Do not accept verbal prescription orders over the phone.

14. Do not dispense refills.

15. Ship dispensed product within 24 hours of receiving the confirmation number or it must be picked up within 24 hours of obtaining the confirmation number.

16. For females (adult and children) who can get pregnant ship THALOMID the same day the confirmation number is obtained, or it must be picked up within 24 hours of obtaining the confirmation number.

17. Report pregnancies immediately to the REMS Program.

18. Do not distribute, transfer, loan, or sell THALOMID, except with the permission of the REMS Program.

19. Maintain records of each prescription dispensed with the corresponding confirmation number, date it was obtained, and completed Education and Counseling Checklist for Pharmacies.

20. Comply with audits carried out by Celgene to ensure that all processes and procedures are in place and are being followed.

21. Accept unused product from the patient or the prescriber.

22. Return unused product from the patient or the prescriber to Celgene.

**Celgene must provide training to healthcare providers who prescribe THALOMID.**

The training must include the following educational materials: Welcome Letter, Prescriber Guide, and REMS Education and Prescribing Safety Kit. The training must be available online and hardcopy format via mail.

**Celgene must provide training to pharmacies that dispense THALOMID.**

The training includes the following educational materials: Pharmacy Guide, Education and Counseling Checklist for Pharmacies, REMS Program Pharmacy Training, and Pharmacy Certification Quiz. The training must be available online and hardcopy format via mail.

**To support REMS Program operations, Celgene must:**

1. Distribute THALOMID only to certified pharmacies.
2. Ensure participating pharmacies are able to certify by contracting with the manufacturer and agreeing to comply with the requirements of the REMS Program.

3. Establish and maintain the REMS Program websites, www.THALOMIDREMS.com and www.celgeneriskmanagement.com. The REMS Program websites must include the capability to complete prescriber certification online, to enroll and to take REMS surveys online, and the option to print the Prescribing Information, Medication Guide, and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program website. The REMS Program website must not link back to the promotional product website(s).


5. Establish and maintain REMS Program call center for REMS participants at 1-888-423-5436.

6. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the REMS Program.

7. Ensure prescribers are able to enroll and enroll patients into the REMS Program by mail, phone, fax, or online.

8. Ensure prescribers are able to complete prescriber surveys by phone and online.

9. Ensure prescribers are able to obtain an authorization number by phone and online. For females who can get pregnant, the authorization is valid for 7 days from the date of the last pregnancy test. For all other patients, the authorization number is valid for 30 days from the date the authorization number is issued.

10. Ensure patients are able to take patient surveys by phone and online.

11. Ensure pharmacies are able to obtain dispense confirmation numbers by phone or online.

12. Ensure prescribers, patients, and pharmacists are able to report pregnancies by phone, mail, fax, and online.

13. Provide Prescriber Enrollment Form, Prescriber Guide and the Prescribing Information to REMS participants who (1) attempt to prescribe THALOMID and are not yet certified or (2) inquire about how to become certified.

14. Notify prescribers within 24 hours after they become certified in the REMS Program.

15. Notify prescribers when patient enrollment is confirmed by fax and online.

16. Provide certified prescribers access to the database of their enrolled patients and certified pharmacies.

17. Provide certified pharmacies access to the REMS system.

18. Establish and maintain a registry which includes a reporting and collection system for female patients or female partners of male patients receiving THALOMID to provide information on pregnancy outcomes and root cause of pregnancy.

19. Ensure that once a report of a pregnancy is received, the THALOMID REMS follows up to obtain all required data for the registry.

To ensure REMS participants’ compliance with the REMS Program, Celgene must:

20. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: THALOMID prescribing and dispensing; enrollment and certification of prescribers and pharmacies; enrollment, appropriate risk categorization, and pregnancy testing results of patients; and audits of pharmacies. These records must be readily available for FDA inspections.

21. Establish a plan for addressing noncompliance with REMS program requirements.
22. Ensure patients who discontinue treatment for 12 consecutive months must re-enroll in the REMS.

23. Monitor prescribers, pharmacies, and patients on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if noncompliance is identified, including de-certification.

24. Monitor and ensure that patients have been assigned correctly to one of the following patient risk categories. Confirm risk category during the patient enrollment process:

- Adult female who can get pregnant: all females who are menstruating, amenorrheic from previous medical treatments, under 50 years, and/or perimenopausal.
- Female child who can get pregnant: all females under 18 years who are menstruating.
- Adult female who cannot get pregnant: females who have had a natural menopause for at least 24 consecutive months, a hysterectomy, and/or bilateral oophorectomy.
- Female child who cannot get pregnant: all females under 18 years who are not menstruating.
- Adult male: 18 years or older
- Male child: under 18 years

25. Audit all pharmacies within 3 months of first dispense of THALOMID, annually for the first 2 years, and at least once every three years thereafter. For pharmacies that have been in the program for more than two years, a risk-based assessment is performed to select which pharmacies are audited.

26. Take reasonable steps to improve implementation of and compliance with the requirements in the THALOMID REMS Program based on monitoring and evaluation of the THALOMID REMS Program.

IV. REMS Assessment Timetable

Celgene must submit REMS assessments August 3, 2015, August 3, 2016 and every two years thereafter. To facilitate inclusion for 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 must submit each assessment so it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the THALOMID REMS:

**Enrollment Forms:**

Prescriber:

1. Prescriber Enrollment Form

Patient:

2. Patient-Physician Agreement Form for Adult Female Who Can Get Pregnant
3. Patient-Physician Agreement Form for Female Child Who Can Get Pregnant
4. Patient-Physician Agreement Form for Adult Female Who Can Not Get Pregnant
5. Patient-Physician Agreement Form for Female Child Who Can Not Get Pregnant
6. Patient-Physician Agreement Form for Adult Male
7. Patient-Physician Agreement Form for Male Child
Training and Educational Materials:

Prescriber:
8. Welcome Letter
9. Prescriber Guide
10. REMS Education and Prescribing Safety Kit

Pharmacy:
11. Pharmacy Guide
12. REMS Program Pharmacy Training
13. Pharmacy Certification Quiz

Patient:
14. Patient Guide
15. Emergency Contraception Brochure

Patient Care Forms
17. Education and Counseling Checklist for Pharmacies

Other Materials
18. REMS Program Website
19. Celgene Risk Management Website