

Risk Evaluation and Mitigation Strategy (REMS) Document

A. REVLIMID¹ REMS Program

I. Administrative Information

Application Number: NDA 021880

Application Holder: Celgene Corporation

Initial REMS Approval: 08/2010

Most Recent REMS Update: **09/2020**

II. REMS Goals

The goals of the REVLIMID REMS are as follows:

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

III. REMS Requirements

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

1. Healthcare providers who prescribe REVLIMID must:	
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To become certified to prescribe	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	3. Review the following: Welcome Letter , Prescriber Guide , and REMS Education and Prescribing Safety Kit .
	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 REVLIMID therapy, including risks described in the Boxed WARNINGS and the need to complete mandatory patient surveys using the Patient Guide and Patient-

¹ The Revlimid-specific requirements contained in this document apply until the date of full approval of the first abbreviated new drug application (ANDA) joining a shared system REMS with REVLIMID.

	<p>Physician Agreement Form (PPAF). Provide a copy of the materials to the patient.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>10. Prescribe no more than a 28 days' supply.</p> <p>11. Not prescribe refills or prescribe over the phone.</p>
During treatment; weekly for at least the first 4 weeks	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.
During treatment; every 2 weeks after the first 4 weeks	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.
During treatment; every 4 weeks after the first 4 weeks	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.
During treatment: before each prescription	<p>15. For all patients: Counsel the patient on the need to complete the patient survey.</p> <p>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.</p> <p>17. For males (adults and children): Counsel the patient on the barrier contraception requirements using the Patient Guide.</p>

	<p>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.</p> <p>19. Prescribe no more than a 28 days' supply.</p> <p>20. Not prescribe refills or prescribe over the phone.</p>
At all times	<p>21. Report any pregnancies in female patients or female partners of male patients immediately to the REMS Program.</p> <p>22. Return all unused product from patients to Celgene.</p>
2. Females (adults and children) who can get pregnant who are prescribed REVLIMID:	
Before treatment initiation; 4 weeks	<p>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.</p>
Before treatment initiation; within 10-14 days and again within 24 hours	<p>2. Get a pregnancy test as directed by your prescriber.</p>
Before treatment initiation	<p>3. Receive counseling from the prescriber on the benefits and risks of REVLIMID therapy and the need to complete the patient survey, on contraception requirements and emergency contraception.</p> <p>4. Review the Patient Guide and the Emergency Contraception Brochure.</p> <p>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 your prescriber. Enrollment information will be provided to the REMS Program.</p> <p>6. Complete the patient survey.</p> <p>7. Receive counseling from the pharmacy on the benefits and risks of REVLIMID; not sharing REVLIMID; not donating blood; not breaking, chewing, or opening REVLIMID capsules; instructions on dose and administration; reading the REVLIMID REMS education materials; and being compliant with the REMS requirements.</p> <p>8. Receive counseling from the pharmacy on the embryo-fetal toxicity with exposure to REVLIMID; contraception requirements; pregnancy testing requirement; not taking REVLIMID if pregnant, breastfeeding, or not using contraception; and to immediately stop taking REVLIMID and notify the prescriber if pregnant or suspect you may be pregnant.</p>

During treatment; weekly at least the first 4 weeks	9. Get a pregnancy test as directed by your prescriber.
During treatment; before each prescription	<p>10. Receive counseling from your prescriber on contraception requirements and emergency contraception and the need to complete the patient survey.</p> <p>11. Get a pregnancy test as directed by your prescriber.</p> <p>12. Receive counseling from the pharmacy on the benefits and risks of REVLIMID; not sharing REVLIMID; not donating blood; not breaking, chewing, or opening REVLIMID capsules; instructions on dose and administration; reading the REVLIMID REMS education materials; and being compliant with the REMS requirements.</p> <p>13. Receive counseling from the pharmacy on embryo-fetal toxicity with exposure to REVLIMID; contraception requirements; pregnancy testing requirement; not taking REVLIMID if pregnant, breastfeeding or not using contraception; and to immediately stop taking REVLIMID and notify the prescriber if pregnant or suspect you may be pregnant.</p> <p>14. Complete the patient survey.</p>
During treatment and after treatment discontinuation; for 4 weeks	<p>15. Adhere to the safe-use conditions: Not donating blood.</p> <p>16. Adhere to the safe-use conditions: Using contraception as described in the Patient Guide and the Patient-Physician Agreement Form; not taking REVLIMID if pregnant, breastfeeding, or not using contraception; and not getting pregnant.</p>
At all times	<p>17. Inform the prescriber if pregnant, miss a menstrual period, experience unusual menstrual bleeding, stop using contraception, or think for any reason that you may be pregnant. Stop taking REVLIMID immediately.</p> <p>18. Return unused REVLIMID to Celgene, your prescriber, or the pharmacy that dispensed your REVLIMID.</p> <p>19. Adhere to safe-use conditions: Not sharing REVLIMID; not breaking, chewing, or opening REVLIMID capsules; and keeping REVLIMID out of reach of children.</p>
3. Adult females who cannot get pregnant who are prescribed REVLIMID:	
Before treatment initiation	<p>1. Receive counseling from the prescriber on the benefits and risks of REVLIMID and the need to complete the patient survey.</p> <p>2. Review the Patient Guide.</p> <p>3. Complete the patient survey.</p> <p>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.</p>

	5. Receive counseling from the pharmacy on the benefits and risks of REVLIMID therapy; not sharing REVLIMID; not donating blood; not breaking, chewing, or opening REVLIMID capsules; instructions on dose and administration; reading the REVLIMID REMS education materials; and being compliant with the REMS requirements.
During treatment; before each prescription	6. Receive counseling from the pharmacy on the benefits and risks of REVLIMID therapy; not sharing REVLIMID; not donating blood; not breaking, chewing, or opening REVLIMID capsules; instructions on dose and administration; reading the REVLIMID REMS education materials; and being compliant with the REMS requirements.
During treatment; every 6 months	7. Receive counseling from the prescriber on the need to complete the patient survey. 8. Complete 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 REVLIMID to Celgene, the prescriber, or the pharmacy that dispensed your REVLIMID. 11. Adhere to the safe-use conditions: Not sharing REVLIMID; not breaking, chewing, or opening REVLIMID capsules; and keeping REVLIMID out of reach of children.
4. Female children who cannot get pregnant who are prescribed REVLIMID:	
Before treatment initiation	1. Receive counseling from the prescriber on the benefits and risks of REVLIMID 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 REVLIMID; not sharing REVLIMID; not donating blood; not breaking, chewing, or opening REVLIMID capsules; instructions on dose and administration; reading the REVLIMID REMS education materials; and being compliant with the REMS requirements. 6. Receive counseling from the pharmacy on informing your REVLIMID prescriber when menses begins.
During treatment; before each prescription	7. Receive counseling from the prescriber on the need to complete the patient survey.

	<ol style="list-style-type: none"> 8. Receive counseling from the pharmacy on the benefits and risks of REVLIMID; not sharing REVLIMID; not donating blood; not breaking, chewing, or opening REVLIMID capsules; instructions on dose and administration; reading the REVLIMID REMS education materials; and being compliant with the REMS requirements. 9. Receive counseling from the pharmacy to inform your REVLIMID prescriber when menses begins. 10. Complete the patient survey.
During treatment and after treatment discontinuation; for 4 weeks	<ol style="list-style-type: none"> 11. Adhere to the safe-use conditions: not donating blood.
At all times	<ol style="list-style-type: none"> 12. Inform your prescriber when menses begins. 13. Return unused REVLIMID to Celgene, your prescriber, or the pharmacy that dispensed your REVLIMID. 14. Adhere to the safe-use conditions: Not sharing REVLIMID; not breaking, chewing, or opening REVLIMID capsules; and keeping REVLIMID out of reach of children.
5. Males (adults and children) who are prescribed REVLIMID:	
Before treatment initiation	<ol style="list-style-type: none"> 1. Receive counseling from the prescriber on the benefits and risks of REVLIMID, the need to complete the patient survey, barrier contraception requirements, and emergency contraception. 2. Review the Patient Guide and the Emergency Contraception Brochure. 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 REVLIMID; not sharing REVLIMID; not donating blood; not breaking, chewing, or opening REVLIMID capsules; instructions on dose and administration; reading the REVLIMID REMS education materials; and being compliant with the REMS requirements. 5. Receive counseling from the pharmacy on embryo-fetal toxicity with exposure to REVLIMID; barrier contraception requirements; and not donating sperm.
During treatment; before each prescription	<ol style="list-style-type: none"> 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 REVLIMID; not sharing REVLIMID; not donating blood; not breaking, chewing, or opening REVLIMID capsules; instructions on dose and administration; reading

	<p>the REVLIMID REMS education materials; and being compliant with the REMS requirements.</p> <p>8. Receive counseling from the pharmacy on embryo-fetal toxicity with exposure to REVLIMID; barrier contraception requirements; and not donating sperm.</p> <p>9. Complete the patient survey.</p>
During treatment and after treatment discontinuation; for 4 weeks	<p>10. Adhere to the safe-use conditions: Using barrier contraception as described in the Patient Guide and Patient-Physician Agreement Form.</p> <p>11. Adhere to the safe-use conditions: Not donating blood or sperm.</p>
At all times	<p>12. Inform the prescriber about unprotected sexual contact with a female who can become pregnant, or about a sexual partner who might be pregnant.</p> <p>13. Return unused REVLIMID to Celgene, your prescriber, or the pharmacy that dispensed your REVLIMID.</p> <p>14. Adhere to safe-use conditions: Not sharing REVLIMID; not breaking, chewing, or opening REVLIMID capsules; and keeping REVLIMID out of reach of children.</p>
6. Pharmacies that dispense REVLIMID must:	
To become certified to dispense	<p>1. Review the following: Pharmacy Guide, REMS Program Pharmacy Training, Pharmacy Certification Quiz.</p> <p>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.</p>
Before dispensing	<p>3. For all patients: Counsel the patient on the benefits and risks of REVLIMID and safe-use conditions using the Education and Counseling Checklist for Pharmacies.</p> <p>4. For females (adult and children) who can get pregnant: counsel on the embryo-fetal toxicity with exposure to REVLIMID and her safe-use conditions using the Education and Counseling Checklist for Pharmacies.</p> <p>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.</p> <p>6. For males (adult and children): Counsel the patient on the embryo-fetal toxicity with exposure to REVLIMID and additional safe-use conditions using the Education and Counseling Checklist for Pharmacies.</p> <p>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.</p>

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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.
 10. Complete the [Education and Counseling Checklist for Pharmacies](#). Retain a completed copy in the patient's record.
 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.
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After dispensing

15. Ship dispensed product within 24 hours of receiving the confirmation number or have it picked up within 24 hours of obtaining the confirmation number.
 16. For females (adult and children) who can get pregnant ship REVLIMID the same day the confirmation number is obtained, or have it picked up within 24 hours of obtaining the confirmation number.
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At all times

17. Report pregnancies immediately to the REMS Program.
 18. Do not distribute, transfer, loan, or sell REVLIMID, except as authorized by 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.
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Celgene must provide training to healthcare providers who prescribe REVLIMID.

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 REVLIMID.

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 REVLIMID 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.REVLIMIDREMS.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).
4. Make the REMS Program websites fully operational and all REMS materials available through www.REVLIMIDREMS.com, www.celgeneriskmanagement.com, and REMS Program call center.
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 REVLIMID 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 REVLIMID to provide information on pregnancy outcomes and root cause of pregnancy.
19. Ensure that once a report of a pregnancy is received, the REVLIMID 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: REVLIMID 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 REVLIMID, 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 REVLIMID REMS Program based on monitoring and evaluation of the REVLIMID 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 REVLIMID 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](#)
16. [Patient Resource Pack Envelope](#)

Patient Care Forms

17. [Education and Counseling Checklist for Pharmacies](#)

Other Materials

18. [REMS Program Website](#)
19. [Celgene Risk Management Website](#)