Prescriber Guide to

Lenalidomide REMS

Risk Evaluation and Mitigation Strategy (REMS)

Due to its structural similarity to thalidomide, a known teratogen, lenalidomide is approved for marketing only under a restricted distribution program approved by the Food and Drug Administration. This program is called Lenalidomide REMS (Risk Evaluation and Mitigation Strategy).

This guide contains important information for prescribers about:

- The risks of lenalidomide, including a Boxed Warning for
  - Embryo-fetal toxicity
  - Hematologic toxicity
  - Venous and arterial thromboembolism
- Lenalidomide REMS
  - Prescriber Certification
  - Patient Enrollment
  - Contraceptive Requirements and Counseling for Patients
  - Initial and Subsequent Prescription Requirements

The Lenalidomide REMS includes both REVLIMID® (lenalidomide) and generic lenalidomide products. The lenalidomide manufacturers have a contractual agreement for administration of the Lenalidomide REMS. All manufacturers retain responsibility for the actions described in the REMS.

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Risks of lenalidomide

Lenalidomide has a Boxed Warning for embryo-fetal toxicity, hematologic toxicity, and deep venous thrombosis (DVT) and pulmonary embolism (PE) as well as risk of myocardial infarction and stroke.

Due to its structural similarity to thalidomide, a known teratogen, lenalidomide is contraindicated in pregnant females or females capable of becoming pregnant. Females of reproductive potential may be treated with lenalidomide if they take adequate precautions to avoid pregnancy.

Lenalidomide is associated with significant neutropenia and thrombocytopenia in patients with del 5q myelodysplastic syndromes (MDS). Many patients taking lenalidomide may require dose interruption and/or reduction. Evaluate your del 5q MDS patients closely for cytopenias. Patients on lenalidomide should have their complete blood counts (CBC) monitored weekly for the first 8 weeks of therapy, and at least monthly thereafter.

There is a significant risk of deep venous thrombosis and pulmonary embolism as well as risk of myocardial infarction and stroke in patients with multiple myeloma (MM) taking lenalidomide plus dexamethasone in combination. Monitor for and advise patients about signs and symptoms of thromboembolism. Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the patient's underlying risks.

This is not a comprehensive description of risks associated with the use of lenalidomide. Please see relevant Prescribing Information, including Boxed WARNINGS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS for further information regarding the use of lenalidomide at www.LenalidomideREMS.com.

Lenalidomide REMS

To avoid embryo-fetal exposure, lenalidomide is only available under a restricted distribution program called "Lenalidomide Risk Evaluation and Mitigation Strategy (REMS)." Only certified prescribers can prescribe lenalidomide and only certified pharmacies can dispense lenalidomide.

In order to receive lenalidomide, all patients must be enrolled in Lenalidomide REMS and agree to comply with the requirements of Lenalidomide REMS. Information about lenalidomide and Lenalidomide REMS can be obtained by visiting **www.LenalidomideREMS.com** or calling the REMS Call Center toll-free at **1-888-423-5436**.

Key points of Lenalidomide REMS

Prescriber

- The prescriber enrolls and becomes certified in Lenalidomide REMS
- The prescriber counsels patient on benefits and risks of lenalidomide
- The prescriber provides contraception and emergency contraception counseling
- The prescriber verifies negative pregnancy test for all female patients of reproductive potential
- The prescriber completes a Lenalidomide REMS Patient-Physician Agreement Form with each patient and sends to Lenalidomide REMS
- The prescriber/patient completes applicable mandatory confidential survey
- The prescriber obtains an authorization number from Lenalidomide REMS and writes it on every prescription, along with the patient risk category
- The prescriber writes no more than a 4-week (28-day) supply, with no automatic refills or telephone prescriptions
- The prescriber sends lenalidomide prescription to certified pharmacy

Pharmacy

- The pharmacy becomes certified in Lenalidomide REMS
- The certified pharmacy must obtain a confirmation number from Lenalidomide REMS before dispensing
- The certified pharmacy dispenses lenalidomide to patient along with a Medication Guide

Prescribing lenalidomide under Lenalidomide REMS

FEMALES

Patient Counseling
Instruct your patients on why and how they and their partners should prevent pregnancy. Also inform them not to share the drug, not to donate blood, and about using 2 effective methods of contraception (at least 1 highly effective method and 1 effective method) at the same time. Patients should be instructed not to extensively handle or open lenalidomide capsules

Pregnancy Tests Only in Females of Reproductive Potential
Conduct initial pregnancy test within 10-14 days. Confirm the patient is not pregnant with a second pregnancy test within 24 hours prior to writing an initial prescription. During treatment, pregnancy testing should be repeated every 4 weeks if the patient has regular menses or is amenorrheic, or every 2 weeks if the patient has irregular menses

Enrollment
Both you and your patients must understand and agree to comply with the requirements of Lenalidomide REMS, including the pregnancy-prevention steps. The Lenalidomide REMS Patient-Physician Agreement Form must be signed by both patient and physician and submitted to Lenalidomide REMS via email (REMSCustomerCare@bms.com), or fax (1-888-432-9325), or electronically at **www.BMSREMSPatientSafety.com/prescriber**. If enrolling a patient online, the system generates an online prescription that you should complete and print, sign (include the authorization number and risk category), and fax to the certified pharmacy

Complete Mandatory Confidential Survey
Your female patients will need to complete a brief survey by phone or online. You will also need to complete a mandatory survey by phone or online, after which you will receive an authorization number. You must complete this survey to obtain a new authorization number every time a lenalidomide prescription is written. Female patients of reproductive potential and all female children must complete surveys monthly in order to obtain subsequent prescriptions. Adult female patients not of reproductive potential must complete surveys every 6 months

MALES

Patient Counseling
Instruct your patients on why and how they and their partners should prevent pregnancy. Also inform them not to share the drug, not to donate blood or sperm, and about appropriate contraceptive use. Patients should be instructed not to extensively handle or open lenalidomide capsules

Enrollment
Both you and your patients must understand and agree to comply with the requirements of Lenalidomide REMS, including the pregnancy-prevention steps. The Lenalidomide REMS Patient-Physician Agreement Form must be signed by both patient and physician and submitted to Lenalidomide REMS via email (REMSCustomerCare@bms.com), or fax (1-888-432-9325), or electronically at **www.BMSREMSPatientSafety.com/prescriber**. If enrolling a patient online, the system generates an online prescription that you should complete and print, sign (include the authorization number and risk category), and fax to the certified pharmacy

Complete Mandatory Confidential Survey
Your male patients will need to complete a brief survey by phone or online. You will also need to complete a mandatory survey by phone or online, after which you will receive an authorization number. You must complete this survey to obtain a new authorization number every time a lenalidomide prescription is written. The *initial survey* is *not required* for male patients, but they must complete surveys monthly in order to obtain subsequent prescriptions

ALL PATIENTS

Fax Prescription Obtain an authorization number from Lenalidomide REMS and write it on the prescription, along with the patient risk category, and then fax it to a certified pharmacy. The certified pharmacy will contact patients for mandatory counseling and coordinate delivery of lenalidomide to them

Lenalidomide REMS patient enrollment

- Obtain, review, and complete the Lenalidomide REMS Patient-Physician Agreement Form online by visiting **www.BMSREMSPatientSafety.com/prescriber** or by calling the REMS Call Center for assistance at **1-888-423-5436**
- Prescribers who do not have access to a computer will be provided with Lenalidomide REMS materials. For additional assistance, please contact Lenalidomide REMS
- Patient, parent/legal guardian, and/or authorized representative must read the Lenalidomide REMS Patient-Physician Agreement Form in the language of their choice

Help ensure timely processing of each prescription

Fill Out Form as Directed

- Write only in the designated areas on the Lenalidomide REMS Patient-Physician Agreement Form
- The box next to each statement must be marked (with an "X") to indicate understanding
- The form must be completed and signed by both prescriber and patient

Instructions for Female Patients

- For female patients, the prescriber will need to provide information on whether the patient has been in surgical menopause, chemical menopause, or natural menopause for at least 24 months

Instructions for Minors

- If the patient is under 18 years of age, his or her legal guardian must read this material, mark the statement in each block of the form (with an "X"), and agree to ensure compliance by signing and dating the form

Instructions for Incompetent Adult Patients

- For an incompetent adult patient, an authorized representative must sign the Lenalidomide REMS Patient-Physician Agreement Form

Lenalidomide REMS patient enrollment (continued)

- 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, mark the statements, and agree to ensure compliance by signing and dating the form
- If the authorized representative does not have the power of attorney, **a signed and dated letter from the prescriber, on the prescriber's letterhead, must be submitted to Lenalidomide REMS, along with the Lenalidomide REMS Patient-Physician Agreement Form.** This letter must contain the following: a statement that the incompetent patient lacks the capacity to complete the Lenalidomide REMS 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 Lenalidomide REMS and is authorized to consent to treatment with lenalidomide on behalf of the patient

Send in Completed Forms

- Send the completed Lenalidomide REMS Patient-Physician Agreement Form online through **www.BMSREMSPatientSafety.com/prescriber** or to Lenalidomide REMS via email (REMSCustomerCare@bms.com), or fax (1-888-432-9325)
- You will receive confirmation electronically or via fax to your office once the patient is enrolled
- Once the Lenalidomide REMS Patient-Physician Agreement Form is received, both female patients and prescriber can take their surveys as required. Male patients do not take initial surveys
- In the event that you do not receive this confirmation within 15 minutes, call the REMS Call Center at **1-888-423-5436**

Note: If therapy with lenalidomide is discontinued for 12 consecutive months, the patient must enroll again in Lenalidomide REMS. Follow the above procedures to re-enroll the patient.

Prescription requirements

All patients

- Provide comprehensive counseling on the benefits and risks of therapy with lenalidomide
- Patients must be counseled on the potential risks of birth defects, other side effects, and important precautions associated with lenalidomide
- Provide counseling not to share lenalidomide capsules, and not to donate blood during treatment (including dose interruptions) and for 4 weeks after receiving their last dose of lenalidomide, as well as counseling on appropriate contraceptive use, including emergency contraception
- Provide patients with educational materials provided in the Lenalidomide REMS Patient Resource Pack
- Patients should be instructed to not extensively handle or open lenalidomide capsules
- Instruct patients to return unused lenalidomide capsules for disposal to Lenalidomide REMS or to their lenalidomide prescriber, or to the pharmacy that dispensed the lenalidomide to them

Female patients

Determine if female patient is of reproductive potential

Two categories:

1. Females of Reproductive Potential

- All females who are menstruating, amenorrheic from previous medical treatments, under 50 years of age, and/or perimenopausal, and do not qualify for the females not of reproductive potential category

2. Females Not of Reproductive Potential

- Females who have been in natural menopause for at least 24 consecutive months, or who have had a hysterectomy and/or bilateral oophorectomy, or female children who have not started menstruating

1. Females of Reproductive Potential

<u>Pregnancy test requirements</u>

- Obtain a **negative** pregnancy test 10 to 14 days prior to writing an initial prescription for lenalidomide and again within 24 hours prior to writing an initial prescription for lenalidomide even if continuous abstinence is the chosen method of birth control
  - The pregnancy test must be sensitive to at least 50 mIU/mL
  - Pregnancy testing should occur weekly during the first 4 weeks of use

Prescription requirements (continued)

- Pregnancy testing should be repeated every 4 weeks if patient has regular menses or is amenorrheic, or every 2 weeks if irregular menses
- If a patient misses her period or if there is any abnormality in menstrual bleeding, lenalidomide should be discontinued immediately. Obtain a pregnancy test and counsel the patient

- **If pregnancy does occur during treatment, lenalidomide must be immediately discontinued.** Any suspected embryo-fetal exposure to lenalidomide must be reported immediately to the FDA via the MedWatch number at **1-800-FDA-1088** and also to the REMS Call Center at **1-888-423-5436**. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling
- The patient must not breastfeed while being treated with lenalidomide

Patient Counseling on Contraception Requirements

Contraception requirements

- Female patients of reproductive potential must either completely abstain from heterosexual sexual contact or must use 2 effective methods of contraception (at least 1 highly effective method and 1 effective method) at the same time
- The 2 effective contraceptive methods include using at the same time at least 1 highly effective method and at least 1 additional method of birth control every time they have sex with a male
- The 2 effective contraceptive methods must be started at least 4 weeks before lenalidomide therapy, during therapy (including dose interruptions), and for at least 4 weeks following discontinuation of therapy

Effective Methods of Birth Control Used at the Same Time

Highly effective birth control methods		Additional effective birth control methods
• Intrauterine device (IUD) • Hormonal methods (birth control pills, hormonal patches, injections, vaginal rings, or implants) • Tubal ligation (having your tubes tied) • Partner's vasectomy (tying of the tubes to prevent the passing of sperm)	+	• Male latex or synthetic condom • Diaphragm • Cervical cap

Prescription requirements (continued)

Remind all patients that not having any sexual intercourse is the only birth control method that is 100% effective.

- **Unacceptable forms of contraception:**
  - Progesterone-only "mini-pills"
  - IUD Progesterone T
  - Female condoms
  - Natural family planning (rhythm method) or breastfeeding
  - Fertility awareness
  - Withdrawal
  - Cervical shield*
- Patients should be counseled that concomitant use of certain prescription drugs and/or dietary supplements can decrease the effects of hormonal contraception. If hormonal or IUD contraception is medically contraindicated, 2 other contraceptive methods may be used simultaneously during periods of concomitant use and for 4 weeks after stopping therapy

2. Females Not of Reproductive Potential

- The patient must confirm that she is currently not pregnant, nor of reproductive potential as she has been in natural menopause for at least 24 months, or had a hysterectomy and/or bilateral oophorectomy
- The parent or guardian must confirm that a prepubertal female child is not now pregnant, nor is of reproductive 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 lenalidomide therapy, during therapy, during dose interruptions, and for at least 4 weeks after stopping therapy

Male patients

- Male patients must be instructed to use a latex or synthetic condom every time they have sexual intercourse with a female of reproductive potential, even if they have undergone a successful vasectomy. The risk to the developing baby from the semen of male patients taking lenalidomide therapy is unknown
- Male patients must be instructed not to donate sperm during treatment (including dose interruptions) and for 4 weeks after their last dose of lenalidomide

Del 5q MDS patients

- Evaluate your del 5q MDS patients closely for cytopenias. Obtain a weekly CBC for the first 8 weeks of treatment, and at least monthly thereafter

*A cervical shield should not be confused with a cervical cap, which is an effective secondary form of contraception.

Initial mandatory confidential survey

Females

- Instruct the female patient to complete a brief initial mandatory confidential survey by visiting **www.BMSREMSPatientSafety.com**, accessing the REMS Companion App, or calling the REMS Call Center at **1-888-423-5436**. See page 12 for subsequent prescription requirements

Males

- Males do not need to take the initial survey

Prescribers

- Prescriber will complete a brief mandatory confidential survey by visiting **www.BMSREMSPatientSafety.com/prescriber** or by calling the REMS Call Center at **1-888-423-5436**, for every patient before each prescription is written. Be prepared to enter some of the following information:
  - Prescriber's identification number
  - Patient's identification number
  - Date and result of patient's pregnancy test(s) (if applicable); valid only for 7 days from date of last pregnancy test
  - Average daily dose
  - Total number of days supply (cannot exceed 28 days)
- An authorization number will be issued upon completion of the survey and must be written along with the patient risk category on the prescription. 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. No automatic refills or telephone prescriptions are permitted

Additional information for the prescriber

- Healthcare provider must send the prescription to a Lenalidomide REMS certified pharmacy. To locate a certified pharmacy, please contact the REMS Call Center at **1-888-423-5436** for the list of pharmacy participants
- Prescribe no more than 4 weeks (28 days) of therapy, with no automatic refills

Subsequent prescription requirements

The prescriber must complete a brief mandatory confidential survey to obtain a new authorization number **every time** a prescription for lenalidomide is written.

No automatic refills or telephone prescriptions are permitted. The patient risk category must be written on the prescription.

Female patients

- Provide counseling as outlined in the "Female patients" section on pages 8-10
- Follow pregnancy test requirements as outlined in "Pregnancy test requirements" section on pages 8-9
- Female patients must complete a brief mandatory confidential survey according to the following schedule:
  - Before prescription is obtained
  - Monthly
    - Adult females of reproductive potential
    - All female children
  - Every 6 months
    - Adult females not of reproductive potential

Male patients

- Provide patient counseling as outlined in the "Male patients" section on page 10
- Male patients must complete a brief mandatory confidential survey once a month
  - Males do not complete an initial survey

Del 5q MDS patients

- Evaluate your del 5q MDS patients closely for cytopenias. Obtain a weekly CBC for the first 8 weeks of treatment and at least monthly thereafter

After the last dose of lenalidomide

After patients have stopped taking lenalidomide, they must do the following:

All patients

- Must not share lenalidomide capsules—especially with females of reproductive potential
- Must return any unused lenalidomide capsules for disposal to Lenalidomide REMS or their lenalidomide prescriber, or to the pharmacy that dispensed the lenalidomide to them
- Must not donate blood for 4 weeks after stopping lenalidomide

Female patients of reproductive potential

- Must not get pregnant for at least 4 weeks after stopping lenalidomide by concurrently using 2 effective methods of contraception (at least 1 highly effective method and 1 effective method) each time engaging in sexual activity with a male

Male patients

- Must use a latex or synthetic condom each time when engaging in sexual activity for 4 weeks after stopping lenalidomide, even if they have undergone a successful vasectomy
- Must not donate sperm for 4 weeks after stopping lenalidomide

Ordering English and non-English materials

Call the REMS Call Center at 1-888-423-5436

- Materials are available in 16 languages and include:
  - Lenalidomide REMS Patient-Physician Agreement Forms
  - Patient Guide to Lenalidomide REMS
  - Mandatory confidential survey forms

Available languages:

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

- The Lenalidomide REMS Patient-Physician Agreement Forms, Patient Guide to Lenalidomide REMS, and mandatory confidential survey forms requested will be faxed directly to the number you indicate. Please be prepared to provide:

Prescriber's:

Name

Identification Number

Full Address

Fax Number

Patient's:

Name

Full Address

Phone Number

Date of Birth

Identification Number

Diagnosis (most recent version of ICD code)

Suspected pregnancy reporting procedure for healthcare professionals

Please report any suspected pregnancy occurring during the treatment with lenalidomide to Lenalidomide REMS using any of the following methods.

Reporting to Lenalidomide REMS

- Online: **www.bms.com/contact**
- Email: **Worldwide.safety@bms.com**
- Toll free: **1-888-423-5436** (REMS Call Center)
- Fax: **1-908-673-9115**

Reporting to the FDA

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

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

For more information about lenalidomide and Lenalidomide REMS, please visit **www.LenalidomideREMS.com** or call the REMS Call Center at **1-888-423-5436**.

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ONC-US-2300025 01/23