

## RASH

# RASH: HOW TO DOSE MODIFY REVIMID

## Dosage modifications for non-hematologic adverse reactions

### REVIMID dose modifications based on rash grade in patients with MM<sup>1</sup>

Grade 1	No dose adjustment required
Grade 2	
Grade 3	Hold treatment and restart at the physician's discretion at next lower dose when toxicity has resolved to Grade 2 or below
Grade 4	Permanently discontinue REVIMID

### Tips for your patients<sup>2\*</sup>

- Wear loose, soft clothing and keep nails short
- Contact HCP immediately if any type of rash is experienced, as intervention may be needed
- Bathe with cool or lukewarm water



### Continue REVIMID treatment until disease progression or unacceptable toxicity<sup>1</sup>

This AE is not the only one you can expect for your patients. Please see the full Prescribing Information for more details.

#### Indications

REVIMID® (lenalidomide) in combination with dexamethasone (dex) is indicated for the treatment of adult patients with multiple myeloma (MM). REVIMID is indicated as maintenance therapy in adult patients with MM following autologous hematopoietic stem cell transplantation (auto-HSCT).

REVIMID is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials.

REVIMID is only available through a restricted distribution program, REVIMID REMS<sup>®</sup>.

#### Selected Safety Information

REVIMID has Boxed WARNINGS for EMBRYO-FETAL TOXICITY, a RESTRICTED DISTRIBUTION PROGRAM—the REVIMID REMS<sup>®</sup>, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM.

**Severe Cutaneous Reactions:** Severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive REVIMID. Consider REVIMID interruption or discontinuation for Grade 2-3 skin rash. Permanently discontinue REVIMID for Grade 4 rash, exfoliative or bullous rash, or for other severe cutaneous reactions such as SJS, TEN, or DRESS.

**Hypersensitivity:** Hypersensitivity including angioedema, anaphylaxis, and anaphylactic reactions to REVIMID has been reported. Permanently discontinue REVIMID for these reactions.

For patients who are auto-HSCT eligible, hematopoietic stem cell mobilization should occur within 4 cycles of receiving REVIMID-containing therapy.

\*For more information, please refer to the American Cancer Society website.

AE, adverse event; auto-HSCT, autologous hematopoietic stem cell transplantation; MM, multiple myeloma.

Please see pullout tab for Important Safety Information and enclosed full Prescribing Information, including Boxed WARNINGS, for REVIMID.



## Important Safety Information

### WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM

#### Embryo-Fetal Toxicity

Do not use REVIMID during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting REVIMID treatment. Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after REVIMID treatment. To avoid embryo-fetal exposure to lenalidomide, REVIMID is only available through a restricted distribution program, the REVIMID REMS<sup>®</sup> program.

Information about the REVIMID REMS program is available at [www.celgeneriskmanagement.com](http://www.celgeneriskmanagement.com) or by calling the manufacturer's toll-free number 1-888-423-5436.

#### Hematologic Toxicity (Neutropenia and Thrombocytopenia)

REVIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q MDS had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q MDS should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors.

#### Venous and Arterial Thromboembolism

REVIMID has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with MM who were treated with REVIMID and dexamethasone therapy. 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.

## CONTRAINDICATIONS

**Pregnancy:** REVIMID can cause fetal harm when administered to a pregnant female and is contraindicated in females who are pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to the fetus.

**Severe Hypersensitivity Reactions:** REVIMID is contraindicated in patients who have demonstrated severe hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide.

## WARNINGS AND PRECAUTIONS

#### Embryo-Fetal Toxicity: See Boxed WARNINGS

- Females of Reproductive Potential: See Boxed WARNINGS.
- Males: Lenalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVIMID and for up to 4 weeks after discontinuing REVIMID, even if they have undergone a successful vasectomy. Male patients taking REVIMID must not donate sperm.
- Blood Donation: Patients must not donate blood during treatment with REVIMID and for 4 weeks following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to REVIMID.

**REVIMID REMS<sup>®</sup> Program: See Boxed WARNINGS:** Prescribers and pharmacies must be certified with the REVIMID REMS program by enrolling and complying with the REMS requirements; pharmacies must only dispense to patients who are authorized to receive REVIMID. Patients must sign a Patient-Physician Agreement Form and comply with REMS requirements; female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements and males must comply with contraception requirements.

**Hematologic Toxicity:** REVIMID can cause significant neutropenia and thrombocytopenia. Monitor patients with neutropenia for signs of infection. Advise patients to observe for bleeding or bruising, especially with use of concomitant medications that may increase risk of bleeding. Patients may require a dose interruption and/or dose reduction. **MM:** Monitor complete blood counts in patients taking REVIMID + dexamethasone or REVIMID as maintenance therapy, every 7 days for the first 2 cycles, on days 1 and 15 of cycle 3, and every 28 days thereafter.

**Venous and Arterial Thromboembolism: See Boxed WARNINGS:** Venous thromboembolic events (DVT and PE) and arterial thromboses (MI and CVA) are increased in patients treated with REVIMID. Patients with known risk factors, including prior thrombosis, may be at greater risk and actions should be taken to try to minimize all modifiable factors (e.g., hyperlipidemia, hypertension, smoking). Thromboprophylaxis is recommended and the regimen should be based on the patient's underlying risks. Erythropoietin-stimulating agents (ESAs) and estrogens may further increase the risk of thrombosis and their use should be based on a benefit-risk decision.

**Increased Mortality in Patients With CLL:** In a clinical trial in the first-line treatment of patients with CLL, single-agent REVIMID therapy increased the risk of death as compared to single-agent chlorambucil. Serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure, occurred more frequently in the REVIMID arm. REVIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials.

**Second Primary Malignancies (SPM):** In clinical trials in patients with MM receiving REVIMID and in patients with FL or MZL receiving REVIMID + rituximab therapy, an increase of hematologic plus solid tumor SPM, notably AML, have been observed. In patients with MM, MDS was also observed. Monitor patients for the development of SPM. Take into account both the potential benefit of REVIMID and risk of SPM when considering treatment.

**Increased Mortality With Pembrolizumab:** In clinical trials in patients with MM, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with MM with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

**Hepatotoxicity:** Hepatic failure, including fatal cases, has occurred in patients treated with REVIMID + dexamethasone. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop REVIMID upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

**Severe Cutaneous Reactions:** Severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive REVIMID. Consider REVIMID interruption or discontinuation for Grade 2-3 skin rash. Permanently discontinue REVIMID for Grade 4 rash, exfoliative or bullous rash, or for other severe cutaneous reactions such as SJS, TEN, or DRESS.

**Tumor Lysis Syndrome (TLS):** Fatal instances of TLS have been reported during treatment with REVIMID. The patients at risk of TLS are those with high tumor burden prior to treatment. Closely monitor patients at risk and take appropriate preventive approaches.

**Tumor Flare Reaction (TFR):** TFR has occurred during investigational use of REVIMID for CLL and lymphoma. Monitoring and evaluation for TFR is recommended in patients with MCL, FL, or MZL. Tumor flare may mimic the progression of disease (PD). In patients with Grade 3 or 4 TFR, it is recommended to withhold treatment with REVIMID until TFR resolves to ≤Grade 1. REVIMID may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician's discretion.

**Impaired Stem Cell Mobilization:** A decrease in the number of CD34+ cells collected after treatment (>4 cycles) with REVIMID has been reported. Consider early referral to transplant center to optimize timing of the stem cell collection.

**Thyroid Disorders:** Both hypothyroidism and hyperthyroidism have been reported. Measure thyroid function before starting REVIMID treatment and during therapy.

Please see additional Important Safety Information on reverse and enclosed full Prescribing Information, including Boxed WARNINGS, for REVIMID.

PULL HERE FOR ADDITIONAL IMPORTANT SAFETY INFORMATION

**Important Safety Information (continued)**

**Early Mortality in Patients With MCL:** In another MCL study, there was an increase in early deaths (within 20 weeks): 12.9% in the REVIMID arm versus 7.1% in the control arm. Risk factors for early deaths include high tumor burden, MIPI score at diagnosis, and high WBC at baseline ( $\geq 10 \times 10^9/L$ ).

**Hypersensitivity:** Hypersensitivity including angioedema, anaphylaxis, and anaphylactic reactions to REVIMID has been reported. Permanently discontinue REVIMID for these reactions.

**ADVERSE REACTIONS****Multiple Myeloma**

- In Newly Diagnosed:** The most frequently reported Grade 3 or 4 reactions included neutropenia, anemia, thrombocytopenia, pneumonia, asthenia, fatigue, back pain, hypokalemia, rash, cataract, lymphopenia, dyspnea, DVT, hyperglycemia, and leukopenia. The highest frequency of infections occurred in Arm Rd Continuous (75%) compared to Arm MPT (56%). There were more Grade 3 and 4 serious adverse reactions of infection in Arm Rd Continuous than either Arm MPT or Rd18.
- The most common adverse reactions reported in  $\geq 20\%$  (Arm Rd Continuous): diarrhea (45%), anemia (44%), neutropenia (35%), fatigue (33%), back pain (32%), asthenia (28%), insomnia (28%), rash (26%), decreased appetite (23%), cough (23%), dyspnea (22%), pyrexia (21%), abdominal pain (20%), muscle spasms (20%), and thrombocytopenia (20%).
- Maintenance Therapy Post Auto-HSCT:** The most frequently reported Grade 3 or 4 reactions in  $\geq 20\%$  (REVIMID arm) included neutropenia, thrombocytopenia, and leukopenia. The serious adverse reactions of lung infection and neutropenia (more than 4.5%) occurred in the REVIMID arm.
- The most frequently reported adverse reactions in  $\geq 20\%$  (REVIMID arm) across both maintenance studies (Study 1, Study 2) were neutropenia (79%, 61%), thrombocytopenia (72%, 24%), leukopenia (23%, 32%), anemia (21%, 9%), upper respiratory tract infection (27%, 11%), bronchitis (4%, 47%), nasopharyngitis (2%, 35%), cough (10%, 27%), gastroenteritis (0%, 23%), diarrhea (54%, 39%), rash (32%, 8%), fatigue (23%, 11%), asthenia (0%, 30%), muscle spasm (0%, 33%), and pyrexia (8%, 20%).

**DRUG INTERACTIONS**

Periodically monitor digoxin plasma levels due to increased  $C_{max}$  and AUC with concomitant REVIMID therapy. Patients taking concomitant therapies such as ESAs or estrogen-containing therapies may have an increased risk of thrombosis. It is not known whether there is an interaction between dexamethasone and warfarin. Close monitoring of PT and INR is recommended in patients with MM taking concomitant warfarin.

**USE IN SPECIFIC POPULATIONS**

- PREGNANCY: See Boxed WARNINGS:** If pregnancy does occur during treatment, immediately discontinue the drug and refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. There is a REVIMID pregnancy exposure registry that monitors pregnancy outcomes in females exposed to REVIMID during pregnancy as well as female partners of male patients who are exposed to REVIMID. This registry is also used to understand the root cause for the pregnancy. Report any suspected fetal exposure to REVIMID to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.
- LACTATION:** There is no information regarding the presence of lenalidomide in human milk, the effects of REVIMID on the breastfed infant, or the effects of REVIMID on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed infants from REVIMID, advise female patients not to breastfeed during treatment with REVIMID.
- RENAL IMPAIRMENT:** Adjust the starting dose of REVIMID based on the creatinine clearance value and for patients on dialysis.

Please see enclosed full Prescribing Information, including Boxed WARNINGS, for REVIMID.



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2.5 - 5 - 10 - 15 - 20 - 25 mg

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**Tips for your patients<sup>2\*</sup>**

- Wear loose, soft clothing and keep nails short
- Bathe with cool or lukewarm water
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**Continue REVIMID treatment until disease progression or unacceptable toxicity<sup>1</sup>**

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- REVIMID has contraindications for Pregnancy and Severe Hypersensitivity Reactions.
- Warnings and Precautions include Embryo-Fetal Toxicity, REVIMID REMS® Program, Hematologic Toxicity, Venous and Arterial Thromboembolism, Increased Mortality in Patients With CLL, Second Primary Malignancies, Increased Mortality With Pembrolizumab, Hepatotoxicity, Severe Cutaneous Reactions, Tumor Lysis Syndrome, Tumor Flare Reaction, Impaired Stem Cell Mobilization, Thyroid Disorders, Early Mortality in Patients With MCL, and Hypersensitivity.

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