

# HOW TO DOSE MODIFY FOR ADVERSE EVENTS

## Patient AE case studies with a focus on rash, fatigue, diarrhea, and neutropenia

Patient cases are hypothetical.

**These AEs are not the only ones you can expect for your patients. Please see the full Prescribing Information for more details.**

### Indications

REVLIMID® (lenalidomide) in combination with dexamethasone (dex) is indicated for the treatment of adult patients with multiple myeloma (MM).

REVLIMID is indicated as maintenance therapy in adult patients with MM following autologous hematopoietic stem cell transplantation (auto-HSCT).

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

REVLIMID is only available through a restricted distribution program, REVLIMID REMS®.

### Selected Safety Information

REVLIMID has Boxed WARNINGS for EMBRYO-FETAL TOXICITY, a RESTRICTED DISTRIBUTION PROGRAM—the REVLIMID REMS®, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM.

See page 2 and full Prescribing Information for complete Boxed WARNINGS.

AE, adverse event.

**Please see Important Safety Information on pages 18-20 and enclosed full Prescribing Information, including Boxed WARNINGS, for REVLIMID.**

  
**Revlimid**<sup>®</sup>  
(lenalidomide) capsules  
2.5 · 5 · 10 · 15 · 20 · 25 mg

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

**Embryo-Fetal Toxicity**

Do not use REVLIMID® (lenalidomide) 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 REVLIMID treatment. Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after REVLIMID treatment. To avoid embryo-fetal exposure to lenalidomide, REVLIMID is only available through a restricted distribution program, the REVLIMID REMS® program.

Information about the REVLIMID 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)**

REVLIMID 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**

REVLIMID 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 REVLIMID 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.

Selected Safety Information (continued)

**CONTRAINDICATIONS**

**Pregnancy:** REVLIMID 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:** REVLIMID 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 REVLIMID and for up to 4 weeks after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm.
- **Blood Donation:** Patients must not donate blood during treatment with REVLIMID 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 REVLIMID.

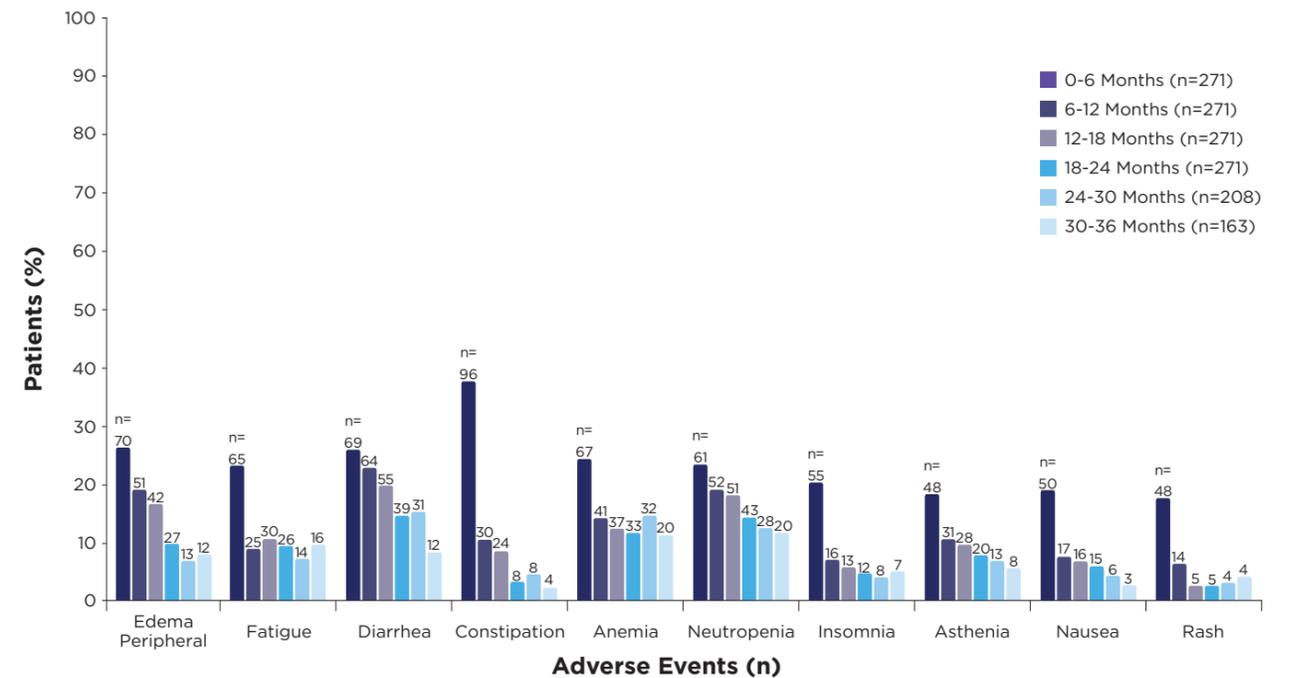
Addressing common adverse events for REVLIMID® (lenalidomide) in MM

In your patients with MM, AEs may be a barrier to optimal adherence. Therefore, it is critical to effectively identify and address AEs related to therapy.<sup>1</sup>

This guide presents common AEs that may occur with REVLIMID through hypothetical patient case studies, providing detailed information on:

- Dose modifications
- Monitoring strategies
- Tips for patients experiencing specific AEs

Common AEs decreased over time in NSCT NDMM in the Rd Continuous arm<sup>2\*</sup>



These AEs are not the only ones you can expect for your patients. Please see the full Prescribing Information for more details.

- The frequency of adverse reactions was generally highest in the first 6 months in both Rd arms and decreased or remained stable over time, except for cataracts
- The frequency of onset of cataracts increased over time with 0.7% during the first 6 months and up to 9.6% by the second year of treatment with Rd Continuous
- Most frequently reported adverse reactions were comparable in the Rd arms
- The most frequently reported adverse reactions included diarrhea, anemia, constipation, peripheral edema, neutropenia, fatigue, back pain, nausea, asthenia, and insomnia
- There were more Grade 3 and 4 serious adverse reactions of infection in the Rd Continuous arm than in either the MPT or Rd18 arms

\*The clinical trial enrolled 1,623 newly diagnosed patients who did not receive a stem-cell transplant. Patients were randomized to receive REVLIMID + low-dose dex (Rd Continuous; n=535) or ≤18 28-day cycles of Rd (Rd18; n=541), or ≤12 42-day cycles of melphalan + prednisone + thalidomide (MPT; n=547). Rd Continuous and Rd18 were dosed as REVLIMID 25 mg once daily on Days 1-21 of 28-day cycles with dex 40 mg on Days 1, 8, 15, and 22. Patients >75 years old received dex 20 mg on Days 1, 8, 15, and 22.<sup>3</sup>

AE, adverse event; dex, dexamethasone; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; NSCT, non-stem cell transplant; Rd, REVLIMID + dexamethasone.

Please see Important Safety Information on pages 18-20 and enclosed full Prescribing Information, including Boxed WARNINGS, for REVLIMID.

## Well-established safety profile in NSCT NDMM<sup>3</sup>

**Trial Design:** FIRST (Frontline Investigation of REVLIMID<sup>®</sup> (lenalidomide) + dexamethasone versus Standard Thalidomide) trial was a randomized, multicenter, open-label, 3-arm study of 1,623 newly diagnosed patients who did not receive a stem-cell transplant. The primary endpoint was PFS and secondary endpoints included OS and response rates. The primary efficacy comparator was REVLIMID + low-dose dex (Rd Continuous) vs ≤12 42-day cycles of MPT. A secondary efficacy comparison was Rd Continuous vs ≤18 28-day cycles of Rd (Rd18). Rd Continuous and Rd18 were dosed as REVLIMID 25 mg once daily on Days 1-21 of 28-day cycles with dex 40 mg on Days 1, 8, 15, and 22. Patients >75 years old received dex 20 mg on Days 1, 8, 15, and 22.

OS was defined as the time from randomization to death from any cause. NE included patients with no response assessment and those whose only assessment was “response not evaluable.”

PFS was defined as the time from randomization to the first documentation of disease progression as determined by Independent Response Adjudication Committee (IRAC), based on International Myeloma Working Group (IMWG) criteria, or death due to any cause, whichever occurred first during the study until the end of the PFS follow-up phase. The data cutoff was May 24, 2013.

### MOST FREQUENTLY REPORTED ADVERSE EVENTS IN ≥20% OF PATIENTS, n (%)<sup>3</sup>

	Rd Continuous (n=532)	Rd18 (n=540)	MPT (n=541)
Fatigue <sup>a</sup>	173 (32.5)	177 (32.8)	154 (28.5)
Asthenia	150 (28.2)	123 (22.8)	124 (22.9)
Pyrexia <sup>b</sup>	114 (21.4)	102 (18.9)	76 (14.0)
Diarrhea	242 (45.5)	208 (38.5)	89 (16.5)
Abdominal pain	109 (20.5)	78 (14.4)	60 (11.1)
Back pain <sup>b</sup>	170 (32)	145 (26.9)	116 (21.4)
Muscle spasms	109 (20.5)	102 (18.9)	61 (11.3)
Anemia	233 (43.8)	193 (35.7)	229 (42.3)
Neutropenia	186 (35.0)	178 (33.0)	328 (60.6)
Thrombocytopenia	104 (19.5)	100 (18.5)	135 (25.0)
Cough	121 (22.7)	94 (17.4)	68 (12.6)
Dyspnea <sup>b</sup>	117 (22.0)	89 (16.5)	113 (20.9)
Decreased appetite	123 (23.1)	115 (21.3)	72 (13.3)
Rash	139 (26.1)	151 (28.0)	105 (19.4)
Insomnia	147 (27.6)	127 (23.5)	53 (9.8)

<sup>a</sup>Adverse reactions in which at least one was considered to be life threatening (if the outcome of the reaction was death, it is included with death cases).

<sup>b</sup>Serious treatment-emergent adverse reactions in at least 1.0% of subjects in the Rd Continuous or Rd18 Arms and at least a 1.0% higher frequency (%) in either the Rd Continuous or Rd18 Arms compared to the MPT Arm.

- 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 the Rd Continuous arm (75%), compared to MPT (56%)

### Selected Safety Information (continued)

**REVLIMID REMS<sup>®</sup> Program: See Boxed WARNINGS:** Prescribers and pharmacies must be certified with the REVLIMID REMS program and complying with the REMS requirements; pharmacies must only dispense to patients who are authorized to receive REVLIMID. 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.

ATE, arterial thromboembolism; auto-HSCT, autologous hematopoietic stem cell transplantation; CALGB, Cancer and Leukemia Group B; dex, dexamethasone; DVT, deep vein thrombosis; IFM, Intergroupe Francophone du Myélome; MM, multiple myeloma; MPT, melphalan + prednisone + thalidomide; NDMM, newly diagnosed multiple myeloma; NE, not evaluable; NSCT, non-stem cell transplant; OS, overall survival; PFS, progression-free survival; Rd, REVLIMID + dexamethasone; VTE, venous thromboembolism.

## Well-established safety profile in maintenance post auto-HSCT<sup>3</sup>

**Trial Design:** CALGB and IFM were multicenter, randomized, double-blind, parallel-group, placebo-controlled studies conducted in newly diagnosed patients between 18 and 70 years (CALGB) and <65 years at diagnosis (IFM) who received auto-HSCT following induction therapy. Patients were required to achieve at least stable disease following hematologic recovery and CrCl ≥30 mL/min. The primary endpoint for both studies was PFS, defined from randomization to the date of progression or death, whichever occurred first. PFS was based on assessment by investigator. At a preplanned interim analysis the primary endpoint of PFS was met and both studies were unblinded. After unblinding, patients continued to be followed as before. In both studies, the starting dose of REVLIMID<sup>®</sup> (lenalidomide) was 10 mg once daily for repeated 28-day cycles. After 3 months, a dose increase to 15 mg once daily occurred in 135 patients (58%) in CALGB, and in 185 patients (60%) in IFM. The dose was reduced, interrupted, and/or discontinued as needed to manage toxicity. Both studies were designed to treat until disease progression, unacceptable toxicity, or patient withdrawal for any reason.

The adverse reactions listed from CALGB (Study 1) included events reported post-transplant (completion of high-dose melphalan/auto-HSCT) and the maintenance treatment period. In IFM (Study 2), the adverse reactions were from the maintenance treatment period only.

### MOST FREQUENTLY REPORTED ADVERSE EVENTS IN ≥20% OF POST AUTO-HSCT PATIENTS, n (%)<sup>2</sup>

	CALGB (Study 1)		IFM (Study 2)	
	REVLIMID (n=224)	Placebo (n=221)	REVLIMID (n=293)	Placebo (n=280)
Neutropenia <sup>a,b</sup>	177 (79.0)	94 (42.5)	178 (60.8)	33 (11.8)
Thrombocytopenia <sup>a,b</sup>	162 (72.3)	101 (45.7)	69 (23.5)	29 (10.4)
Leukopenia <sup>a</sup>	51 (22.8)	25 (11.3)	93 (31.7)	21 (7.5)
Anemia	47 (21.0)	27 (12.2)	26 (8.9)	15 (5.4)
Upper respiratory tract infection	60 (26.8)	35 (15.8)	32 (10.9)	18 (6.4)
Bronchitis <sup>a</sup>	10 (4.5)	9 (4.1)	139 (47.4)	104 (37.1)
Nasopharyngitis	5 (2.2)	2 (0.9)	102 (34.8)	84 (30.0)
Gastroenteritis <sup>a</sup>	0 (0.0)	0 (0.0)	66 (22.5)	55 (19.6)
Diarrhea	122 (54.5)	83 (37.6)	114 (38.9)	34 (12.1)
Fatigue	51 (22.8)	30 (13.6)	31 (10.6)	15 (5.4)
Asthenia	0 (0.0)	1 (0.5)	87 (29.7)	53 (18.9)
Pyrexia	17 (7.6)	10 (4.5)	60 (20.5)	26 (9.3)
Rash	71 (31.7)	48 (21.7)	22 (7.5)	17 (6.1)
Muscle spasms	0 (0.0)	1 (0.5)	98 (33.4)	43 (15.4)
Cough	23 (10.3)	12 (5.4)	80 (27.3)	56 (20.0)

<sup>a</sup>All serious treatment-emergent AEs (adverse events) were in at least 1% of patients in the lenalidomide maintenance group and at least 1% higher frequency (%) than the placebo maintenance group.

<sup>b</sup>ADRs (adverse drug reactions) where at least one was considered to be life threatening (if the outcome of the event was death, it is included with death cases).

- The most frequently reported Grade 3 or 4 adverse reactions (>20% in the REVLIMID arm) included neutropenia, thrombocytopenia, and leukopenia
- In the MM maintenance therapy trials, Grade 3 or 4 neutropenia was reported in up to 59% of REVLIMID-treated patients and Grade 3 or 4 thrombocytopenia in up to 38% of REVLIMID-treated patients
- VTE and ATE are increased in patients treated with REVLIMID
  - Prophylactic medications (aspirin, heparin, or warfarin) could be prescribed for patients at high risk for thrombosis in CALGB<sup>2</sup>
  - Protocol did not include systematic thromboprophylaxis in IFM<sup>2</sup>
- The serious adverse reactions, lung infection and neutropenia (>4.5%), occurred in the REVLIMID arm

**Please see Important Safety Information on pages 18-20 and enclosed full Prescribing Information, including Boxed WARNINGS, for REVLIMID.**

# REVLIMID® (lenalidomide) patient presenting with rash and fatigue

## Emily

Patient with NSCT NDMM on REVLIMID + dex

Hypothetical patient case.



### Patient history and presentation

- 75 years of age
- Diagnosed with multiple myeloma
- Comorbidities: Hypertension (controlled with meds) and history of disk herniation

### Baseline evaluation

- IgG: 5500 mg/dL (High)
- M-protein: 4.5 g/dL (High)
- BMPCs: 70%
- CrCl: 62 mL/min
- Imaging: 1-2 small lytic lesions
- Performance status: 1

### Treatment plan

- Emily was not eligible for stem cell transplant and was prescribed REVLIMID 25 mg + dex\*

### Selected Safety Information (continued)

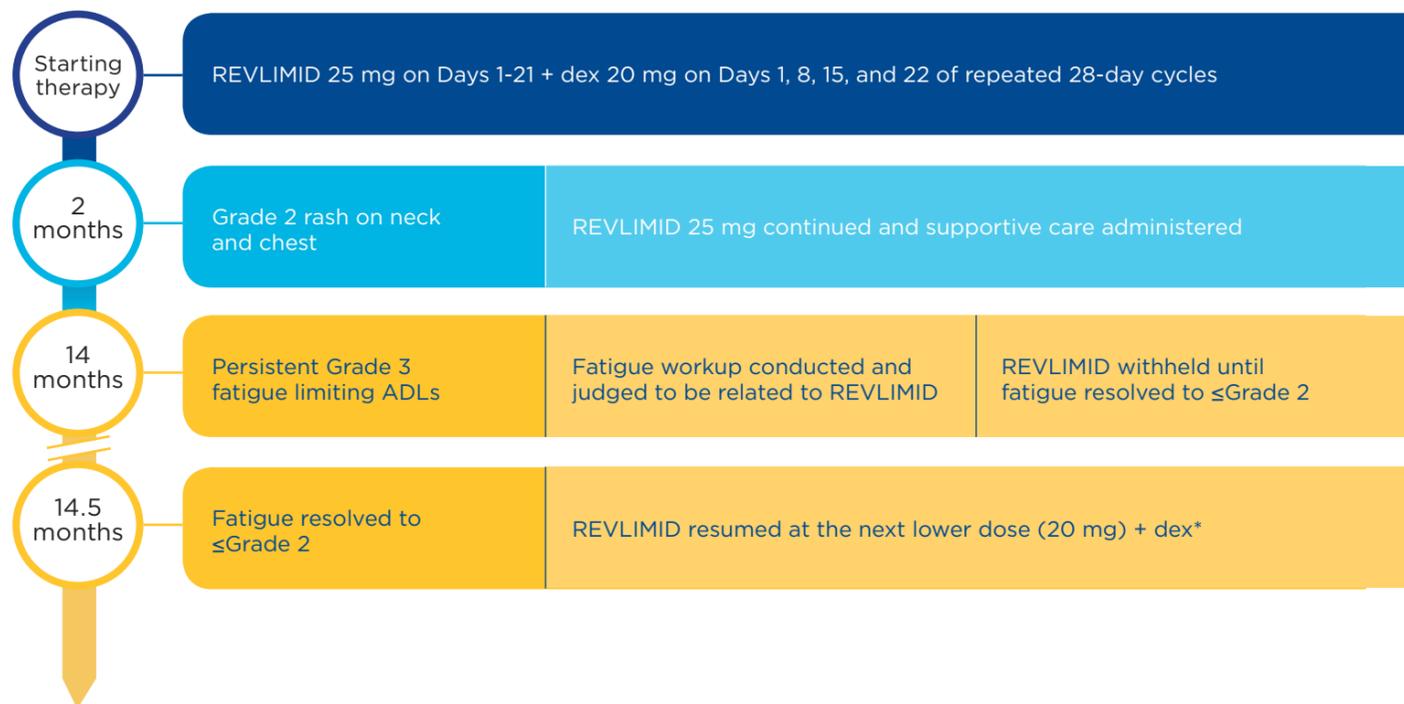
**Hematologic Toxicity:** REVLIMID can cause significant neutropenia and thrombocytopenia. Monitor patients with neutropenia for signs of infection. Advise patients to observe for bleeding or bruising, especially with use of concomitant medications that may increase risk of bleeding. Patients may require a dose interruption and/or dose reduction. **MM:** Monitor complete blood counts in patients taking REVLIMID + dexamethasone or REVLIMID 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 REVLIMID. 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.

ADL, activities of daily living; BMPCs, bone marrow plasma cells; CrCl, creatinine clearance; dex, dexamethasone; IgG, immunoglobulin G; M-protein, monoclonal protein; NDMM, newly diagnosed multiple myeloma; NSCT, non-stem cell transplant.

## Addressing Emily's rash and fatigue

Emily was not eligible for stem cell transplant and was prescribed REVLIMID® (lenalidomide) 25 mg + dex\*



- Permanently discontinue REVLIMID for angioedema, anaphylaxis, Grade 4 rash, skin exfoliation, bullae, or any other severe dermatologic reactions<sup>3</sup>

### Tips for patients experiencing rash<sup>4</sup>

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

### Tips for patients experiencing fatigue<sup>5</sup>

- Limit naps to ≤30 minutes
- Increase physical activity; schedule activities at peak energy
- Discuss nutrition with the healthcare team

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

\*REVLIMID on Days 1-21 and dex 20 mg on Days 1, 8, 15, and 22 of repeated 28-day cycles.

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# Rash and fatigue: How to dose modify REVLIMID® (lenalidomide)

## Dosage modifications for non-hematologic adverse reactions

REVLIMID dose modifications based on rash grade in patients with MM <sup>6</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 REVLIMID	



Help patients stay on therapy with dose modifications<sup>3\*</sup>

REVLIMID dose modifications based on fatigue grade in patients with MM <sup>3,6</sup>	
Grade 1: Mild fatigue over baseline	No dose adjustment required
Grade 2: Moderate or causing difficulty performing some ADL	
Grade 3: Severe fatigue interfering with ADL	Hold treatment and restart at the physician's discretion at next lower dose when toxicity has resolved to Grade 2 or below
Grade 4: Disabling	

The severity of AEs was graded by CTCAE v3.0 in the FIRST Trial and Maintenance Study 1. Maintenance Study 2 used the WHO toxicity criteria to grade adverse events.<sup>†‡</sup>

### Selected Safety Information (continued)

**Increased Mortality in Patients With CLL:** In a clinical trial in the first-line treatment of patients with CLL, single-agent REVLIMID 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 REVLIMID arm. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials.

\*Until disease progression or unacceptable toxicity.

†The FIRST Trial enrolled 1,623 patients with NDMM who did not receive a stem-cell transplant. Patients were randomized to receive REVLIMID + low-dose dex (Rd Continuous; n=535) or ≤18 28-day cycles of Rd (Rd18; n=541), or ≤12 42-day cycles of melphalan + prednisone + thalidomide (MPT; n=547). Rd Continuous and Rd18 were dosed as REVLIMID 25 mg once daily on Days 1-21 of 28-day cycles with dex 40 mg on Days 1, 8, 15, and 22. Patients >75 years old received dex 20 mg on Days 1, 8, 15, and 22.<sup>3</sup>

‡Maintenance Study 1 (US, N=460) and Maintenance Study 2 (EU, N=614) were randomized, double-blind, placebo-controlled studies evaluating REVLIMID Maintenance in patients with newly diagnosed MM who received an auto-HSCT following induction therapy. In both studies, the starting dose of REVLIMID was 10 mg once daily for repeated 28-day cycles.<sup>3</sup>

ADL, activities of daily living; AE, adverse event; auto-HSCT, autologous hematopoietic stem cell transplantation; CTCAE, Common Terminology Criteria for Adverse Events; dex, dexamethasone; FIRST, Frontline Investigation of REVLIMID + dexamethasone versus Standard Thalidomide; MM, multiple myeloma; WHO, World Health Organization.

## Notes



Please see Important Safety Information on pages 18-20 and enclosed full Prescribing Information, including Boxed WARNINGS, for REVLIMID® (lenalidomide).

# REVLIMID® (lenalidomide) patient presenting with diarrhea and fatigue

## Glen

Patient with MM on REVLIMID Maintenance post auto-HSCT

Hypothetical patient case.



### Patient history and presentation

- 64 years of age
- Presented with anemia
- Diagnosed with multiple myeloma
- Comorbidities: Hip dislocation and asthma

### Baseline evaluation

- IgG: 2500 mg/dL (High)
- Hgb: 9.6 g/dL (Low)
- Hematocrit: 32.7% (Low)
- M-protein: 2.1 g/dL (High)
- BMPCs: 60%
- Performance status: 1

### Treatment plan

- Glen received induction therapy and underwent auto-HSCT
- REVLIMID Maintenance therapy is started at hematologic recovery. Hematologic recovery: ANC  $\geq$ 1000/mcL and/or platelet counts  $\geq$ 75,000/mcL<sup>3</sup>
- He was prescribed REVLIMID 10 mg for maintenance therapy, which was increased after 3 cycles to 15 mg

### Selected Safety Information (continued)

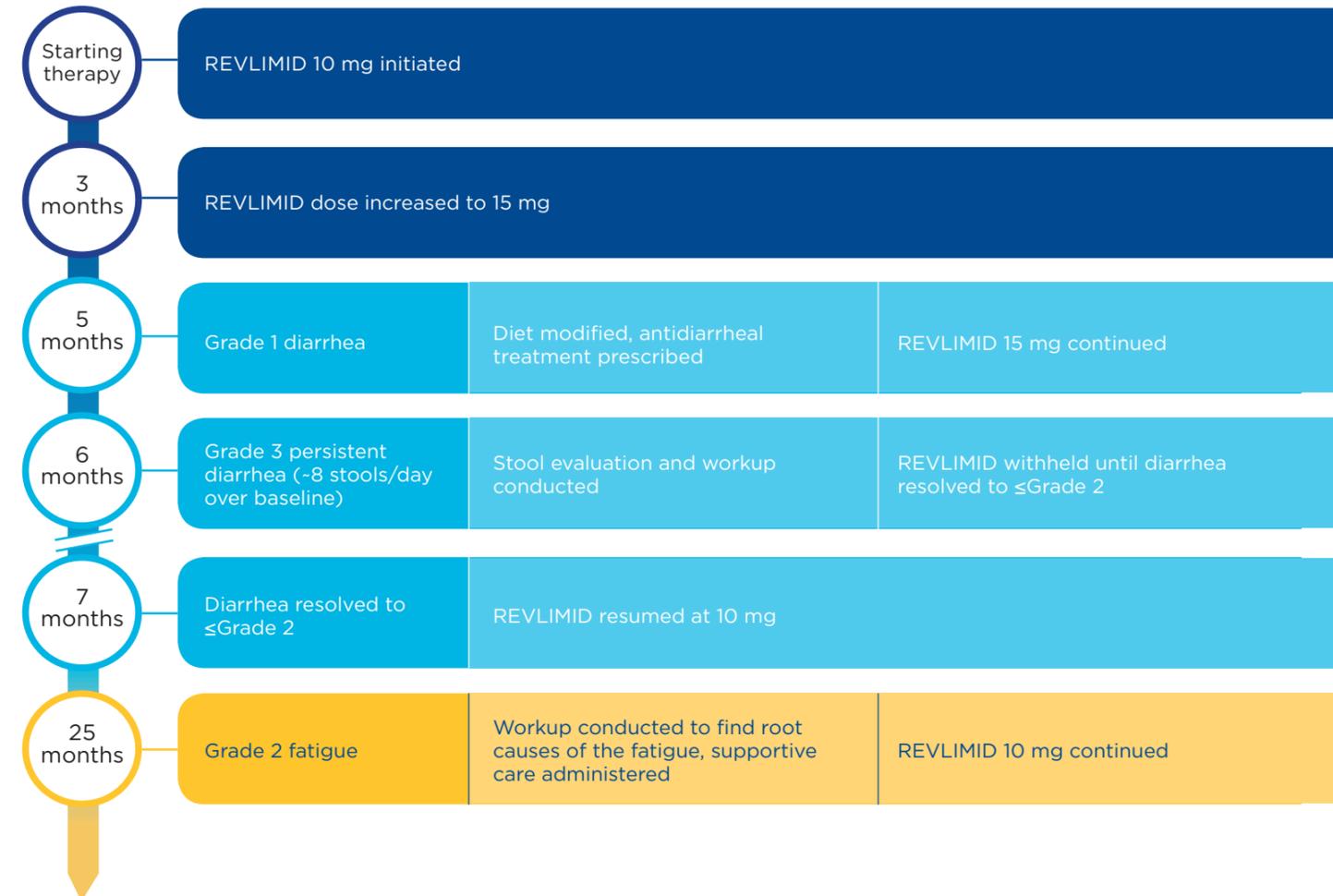
**Second Primary Malignancies (SPM):** In clinical trials in patients with MM receiving REVLIMID and in patients with FL or MZL receiving REVLIMID + rituximab therapy, an increase of hematologic plus solid tumor SPM, notably AML, have been observed. In patients with MM, MDS was also observed. Monitor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

ANC, absolute neutrophil count; auto-HSCT, autologous hematopoietic stem cell transplantation; BMPCs, bone marrow plasma cells; Hgb, hemoglobin; IgG, immunoglobulin G; M-protein, monoclonal protein; MM, multiple myeloma.

## Addressing Glen's diarrhea and fatigue

Glen was prescribed REVLIMID® (lenalidomide) Maintenance following his auto-HSCT and hematologic recovery



### Tips for patients experiencing diarrhea<sup>7</sup>

- Drink  $\geq$ 1 cup of liquid after each loose bowel movement
- Consider antidiarrheals
- Be sure diet includes foods that are high in potassium (such as bananas, potatoes, apricots, and sports drinks)

For additional information on patients experiencing fatigue, please refer to page 7.

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

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# REVLIMID® (lenalidomide) patient presenting with neutropenia

## Mike

Patient with MM on REVLIMID Maintenance post auto-HSCT

Hypothetical patient case.



### Patient history and presentation

- 68 years of age
- Presented with back pain
- Diagnosed with multiple myeloma
- Comorbidity: Arthrosis

### Baseline evaluation

- IgA: 3200 mg/dL (High)
- M-protein: 2.5 g/dL (High)
- ANC: 2500/mcL
- BMPCs: 40%
- Imaging: Negative/Normal
- Performance status: 0

### Treatment plan

- Mike received induction therapy and underwent auto-HSCT
- REVLIMID Maintenance therapy is started at hematologic recovery. Hematologic recovery: ANC  $\geq$ 1000/mcL and/or platelet counts  $\geq$ 75,000/mcL<sup>3</sup>
- He was prescribed REVLIMID 10 mg for maintenance therapy following hematologic recovery

### Selected Safety Information (continued)

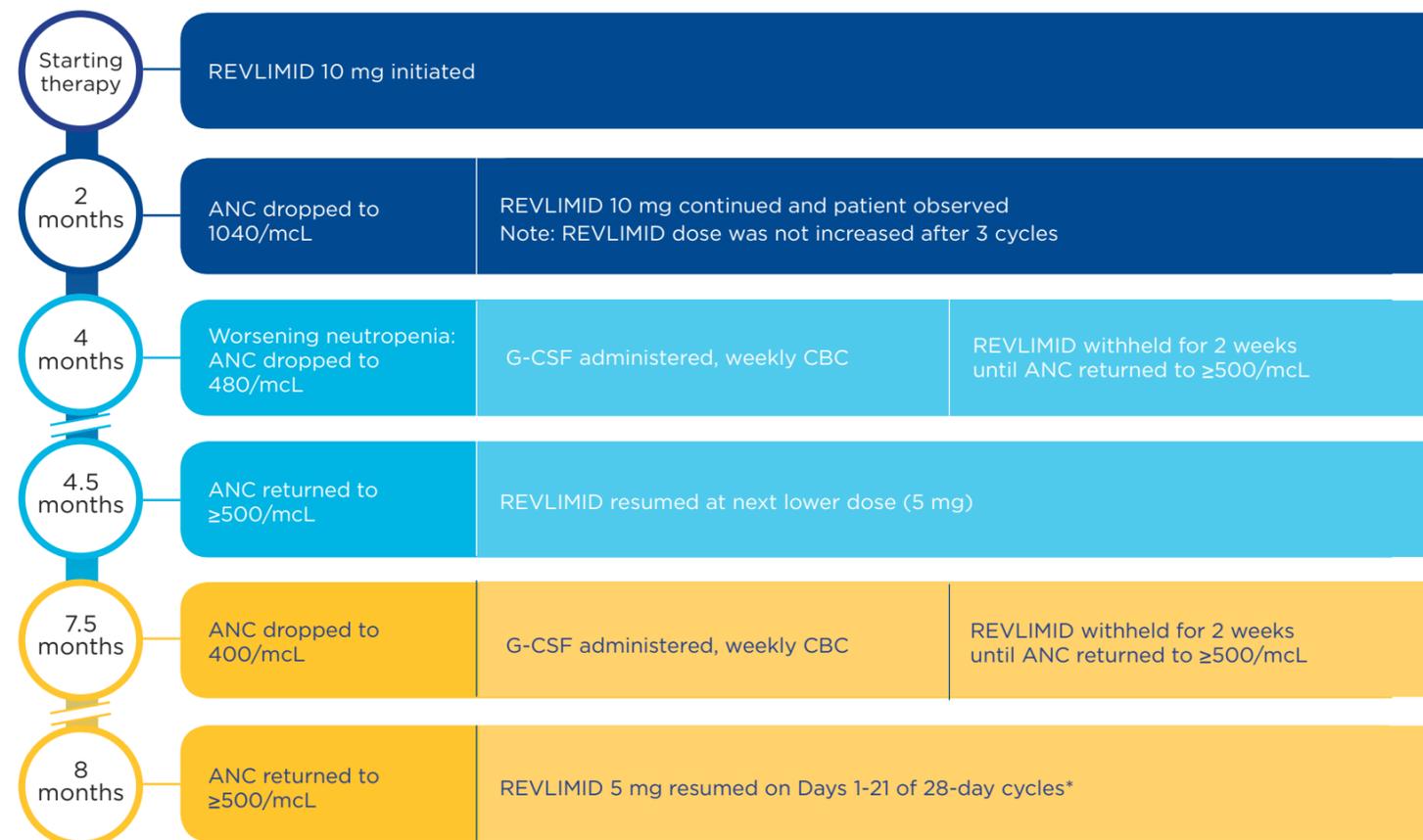
**Tumor Lysis Syndrome (TLS):** Fatal instances of TLS have been reported during treatment with REVLIMID. The patients at risk of TLS are those with high tumor burden prior to treatment. Closely monitor patients at risk and take appropriate preventive approaches.

**Tumor Flare Reaction (TFR):** TFR has occurred during investigational use of REVLIMID 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 REVLIMID until TFR resolves to  $\leq$ Grade 1. REVLIMID may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician's discretion.

ANC, absolute neutrophil count; auto-HSCT, autologous hematopoietic stem cell transplantation; BMPCs, bone marrow plasma cells; CBC, complete blood count; G-CSF, granulocyte colony-stimulating factor; IgA, immunoglobulin A; M-protein, monoclonal protein; MM, multiple myeloma.

# Addressing Mike's neutropenia

Mike was prescribed REVLIMID® (lenalidomide) Maintenance following his auto-HSCT and hematologic recovery



### Monitoring your patients<sup>3</sup>

- Check CBCs
  - Every 7 days for the first 2 cycles
  - On Days 1 and 15 of Cycle 3
  - Every 28 days thereafter

### Physical examination<sup>8</sup>

- Observe the oral mucosa and skin for breaks in tissue and signs of infection
- If a patient has a central venous access device, assess the exit site for erythema or exudate

### Tips for patients experiencing neutropenia<sup>9</sup>

- Contact HCP if experiencing any signs of infection (eg, fever, diarrhea, mouth sores, bloody urine)
- Wash hands frequently with soap and warm water

For more information, please refer to the *Clinical Journal of Oncology Nursing* and the National Cancer Institute website.

\*REVLIMID is not dosed below 5 mg daily on Days 1-21 of 28-day cycles.

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## Important Safety Information

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REVLIMID is indicated as maintenance therapy in adult patients with MM following autologous hematopoietic stem cell transplantation (auto-HSCT).

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

#### Embryo-Fetal Toxicity

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Information about the REVLIMID 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)

REVLIMID 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

REVLIMID 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 REVLIMID 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:** REVLIMID 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:** REVLIMID 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 REVLIMID and for up to 4 weeks after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm.
- **Blood Donation:** Patients must not donate blood during treatment with REVLIMID 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 REVLIMID.

Please see additional Important Safety Information on pages 19 and 20 and enclosed full Prescribing Information, including Boxed WARNINGS, for REVLIMID.

## Important Safety Information (continued)

**REVLIMID REMS® Program: See Boxed WARNINGS:** Prescribers and pharmacies must be certified with the REVLIMID REMS program by enrolling and complying with the REMS requirements; pharmacies must only dispense to patients who are authorized to receive REVLIMID® (lenalidomide). 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:** REVLIMID 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 REVLIMID + dexamethasone or REVLIMID 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 REVLIMID. 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 REVLIMID 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 REVLIMID arm. REVLIMID 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 REVLIMID and in patients with FL or MZL receiving REVLIMID + 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 REVLIMID 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 REVLIMID + dexamethasone. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop REVLIMID 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 REVLIMID. Consider REVLIMID interruption or discontinuation for Grade 2-3 skin rash. Permanently discontinue REVLIMID 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 REVLIMID. 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 REVLIMID 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 REVLIMID until TFR resolves to ≤Grade 1. REVLIMID 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 REVLIMID 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 REVLIMID treatment and during therapy.

**Early Mortality in Patients With MCL:** In another MCL study, there was an increase in early deaths (within 20 weeks); 12.9% in the REVLIMID 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 REVLIMID has been reported. Permanently discontinue REVLIMID for these reactions.

Please see additional Important Safety Information on pages 18 and 20 and enclosed full Prescribing Information, including Boxed WARNINGS, for REVLIMID.

# Important Safety Information (continued)

## 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 and 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  $\geq 20\%$  (REVLIMID® (lenalidomide) arm) included neutropenia, thrombocytopenia, and leukopenia. The serious adverse reactions of lung infection and neutropenia (more than 4.5%) occurred in the REVLIMID arm.
- The most frequently reported adverse reactions in  $\geq 20\%$  (REVLIMID 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 REVLIMID 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 REVLIMID pregnancy exposure registry that monitors pregnancy outcomes in females exposed to REVLIMID during pregnancy as well as female partners of male patients who are exposed to REVLIMID. This registry is also used to understand the root cause for the pregnancy. Report any suspected fetal exposure to REVLIMID 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 REVLIMID on the breastfed infant, or the effects of REVLIMID on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed infants from REVLIMID, advise female patients not to breastfeed during treatment with REVLIMID.
- RENAL IMPAIRMENT:** Adjust the starting dose of REVLIMID based on the creatinine clearance value and for patients on dialysis.

# References

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# Help patients stay on therapy with dose modifications<sup>3</sup>

With appropriate dose modifications, patient monitoring, and supportive care, you may address common AEs related to REVLIMID therapy



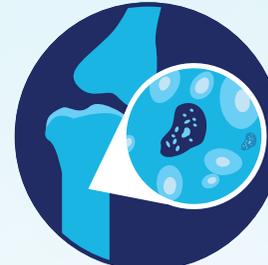
Rash



Diarrhea



Fatigue



Neutropenia

These AEs are not the only ones you can expect for your patients. Please see the full Prescribing Information for more details.

See full Prescribing Information for dose modifications.



Continue REVLIMID treatment until disease progression or unacceptable toxicity<sup>3</sup>

## Selected Safety Information

REVLIMID has Boxed WARNINGS for EMBRYO-FETAL TOXICITY, a RESTRICTED DISTRIBUTION PROGRAM—the REVLIMID REMS®, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM.

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

AE, adverse event.

Please see Important Safety Information on pages 18-20 and enclosed full Prescribing Information, including Boxed WARNINGS, for REVLIMID.



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**Revlimid<sup>®</sup>**  
(lenalidomide) capsules  
2.5 · 5 · 10 · 15 · 20 · 25 mg