HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use REVLIMID® safely and effectively. See full prescribing information for REVLIMID.

REVLIMID [lenalidomide] capsules, for oral use
Initial U.S. Approval: 2005

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM
See full prescribing information for complete boxed warning.

EMBRYO-FETAL TOXICITY

- **Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death.**
- **Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception (5.1).**

REVLIMID is available only through a restricted distribution program called the REVLIMID REMS® program (5.2, 17).

HEMATOLOGIC TOXICITY. REVLIMID can cause significant neutropenia and thrombocytopenia (5.3).

- **For patients with del 5q myelodysplastic syndromes, monitor complete blood counts weekly for the first 8 weeks and monthly thereafter (5.3).**

VENOUS AND ARTERIAL THROMBOEMBOLISM

- **Significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with multiple myeloma receiving REVLIMID with dexamethasone. Anti-thrombotic prophylaxis is recommended (5.4).**

----------RECENT MAJOR CHANGES----------

Indication and Usage (1.1)	02/17
Dosage and Administration (2.1, 2.4)	02/17
Warnings and Precautions (5.3, 5.4, 5.6, 5.9, 5.13, 5.14)	09/17
Warnings and Precautions (5.7)	12/17

----------INDICATIONS AND USAGE----------

REVLIMID is a thalidomide analogue indicated for the treatment of patients with:

- Multiple myeloma (MM), in combination with dexamethasone (1.1).
- MM, as maintenance following autologous hematopoietic stem cell transplantation (auto-HSCT) (1.1).
- Transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities (1.2).
- Mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib (1.3).

Limitations of Use:

- REVLIMID is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials (1.4).

----------DOSAGE AND ADMINISTRATION----------

- MM combination therapy: 25 mg once daily orally on Days 1-21 of repeated 28-day cycles. Refer to section 14.1 for dexamethasone dosing (2.1, 14.1).
- MM maintenance therapy following auto-HSCT: 10 mg once daily continuously on Days 1-28 of repeated 28-day cycles (2.1).
- MDS: 10 mg once daily (2.2).
- MCL: 25 mg once daily orally on Days 1-21 of repeated 28-day cycles (2.3).
- Continue or modify dosing based on clinical and laboratory findings (2.1, 2.2, 2.3).
- Renal impairment: Adjust starting dose based on the creatinine clearance value (2.4).

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg (3).

----------CONTRAINDICATIONS----------

- Pregnancy (Boxed Warning, 4.1, 5.1, 8.1).
- Demonstrated severe hypersensitivity to lenalidomide (4.2, 5.9).

----------WARNINGS AND PRECAUTIONS----------

- Increased mortality: serious and fatal cardiac adverse reactions occurred in patients with CLL treated with REVLIMID (5.5).
- Second Primary Malignancies (SPM): Higher incidences of SPM were observed in controlled trials of patients with MM receiving REVLIMID (5.6).
- Increased Mortality: Observed in patients with MM when pembrolizumab was added to dexamethasone and a thalidomide analogue (5.7).
- Hepatotoxicity: Hepatic failure including fatalities; monitor liver function. Stop REVLIMID and evaluate if hepatotoxicity is suspected (5.8).
- Cutaneous Reactions, including fatalities: Hypersensitivity, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms; discontinue REVLIMID if reactions are suspected. Do not resume REVLIMID if these reactions are verified (5.9).
- Tumor lysis syndrome (TLS) including fatalities: Monitor patients at risk of TLS (i.e., those with high tumor burden) and take appropriate precautions (5.10).
- Tumor flare reaction: Serious tumor flare reactions have occurred during investigational use of REVLIMID for chronic lymphocytic leukemia and lymphoma (5.11).
- 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 (5.12).
- Early mortality in MCL: Higher rate of early deaths have occurred in patients with MCL (5.14).

----------ADVERSE REACTIONS----------

- MM: Most common adverse reactions (≥20%) include diarrhea, fatigue, anemia, constipation, neutropenia, leukopenia, peripheral edema, insomnia, muscle cramp/spasms, abdominal pain, back pain, nausea, asthenia, pyrexia, upper respiratory tract infection, bronchitis, nasopharyngitis, gastroenteritis, cough, rash, dyspnea, dizziness, decreased appetite, thrombocytopenia, and tremor (6.1).
- MDS: Most common adverse reactions (>15%) include thrombocytopenia, neutropenia, diarrhea, pruritus, rash, fatigue, constipation, nausea, nasopharyngitis, arthralgia, pyrexia, back pain, peripheral edema, cough, dizziness, headache, muscle cramp, dyspnea, pharyngitis, and epistaxis (6.1).
- MCL: Most common adverse reactions (≥15%) include neutropenia, thrombocytopenia, fatigue, diarrhea, anemia, nausea, cough, pyrexia, rash, dyspnea, pruritus, constipation, peripheral edema and leukopenia (6.1).

To report SUSPECTED ADVERSE REACTIONS contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Digoxin: Periodic monitoring of digoxin plasma levels is recommended due to increased C_{max} and AUC with concomitant REVLIMID therapy (7.1).
- Patients taking concomitant therapies such as erythropoietin stimulating agents or estrogen containing therapies may have an increased risk of thrombosis (7.2).

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise women not to breastfeed. (8.2).
- Renal Impairment: Adjust the starting dose of REVLIMID for patients based on creatinine clearance value (2.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 12/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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

Embryo-Fetal Toxicity

Do not use REVLIMID 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 *[see Warnings and Precautions (5.1), and Medication Guide (17)]*. To avoid embryo-fetal exposure to lenalidomide, REVLIMID is only available through a restricted distribution program, the REVLIMID REMS® program (5.2).

Information about the REVLIMID REMS program is available at 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 myelodysplastic syndromes 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 myelodysplastic syndromes 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 *[see Dosage and Administration (2.2)]*.

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 multiple myeloma 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 *[see Warnings and Precautions (5.4)]*.

1 INDICATIONS AND USAGE

1.1 Multiple Myeloma

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

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

1.2 Myelodysplastic Syndromes

REVLIMID is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

1.3 Mantle Cell Lymphoma

REVLIMID is indicated for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.

1.4 Limitations of Use

REVLIMID is not indicated and is not recommended for the treatment of patients with CLL outside of controlled clinical trials *[see Warnings and Precautions (5.5)]*.

2 DOSAGE AND ADMINISTRATION

REVLIMID should be taken orally at about the same time each day, either with or without food. REVLIMID capsules should be swallowed whole with water. The capsules should not be opened, broken, or chewed.

2.1 Multiple Myeloma

REVLIMID Combination Therapy

The recommended starting dose of REVLIMID is 25 mg orally once daily on Days 1-21 of repeated 28-day cycles in combination with dexamethasone. Refer to Section 14.1 for specific dexamethasone dosing. For patients > 75 years old, the starting dose of dexamethasone may be reduced *[see Clinical Studies (14.1)]*. Treatment should be continued until disease progression or unacceptable toxicity.

In patients who are not eligible for auto-HSCT, treatment should continue until disease progression or unacceptable toxicity. For patients who are auto-HSCT-eligible, hematopoietic stem cell mobilization should occur within 4 cycles of a REVLIMID-containing therapy *[see Warnings and Precautions (5.12)]*.

Dose Adjustments for Hematologic Toxicities During MM Treatment

Dose modification guidelines, as summarized in Table 1 below, are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicity judged to be related to REVLIMID.

Table 1: Dose Adjustments for Hematologic Toxicities for MM

Platelet counts

Thrombocytopenia in MM

When Platelets	Recommended Course Days 1-21 of repeated 28-day cycle
Fall to <30,000/mcL Return to ≥30,000/mcL	Interrupt REVLIMID treatment, follow CBC weekly Resume REVLIMID at next lower dose. Do not dose below 2.5 mg daily
For each subsequent drop <30,000/mcL Return to ≥30,000/mcL	Interrupt REVLIMID treatment Resume REVLIMID at next lower dose. Do not dose below 2.5 mg daily

Absolute Neutrophil counts (ANC)

Neutropenia in MM

When Neutrophils	Recommended Course Days 1-21 of repeated 28-day cycle
Fall to <1000/mcL Return to ≥1,000/mcL and neutropenia is the only toxicity	Interrupt REVLIMID treatment, follow CBC weekly Resume REVLIMID at 25 mg daily or initial starting dose
Return to ≥1,000/mcL and if other toxicity	Resume REVLIMID at next lower dose. Do not dose below 2.5 mg daily
For each subsequent drop <1,000/mcL Return to ≥1,000/mcL	Interrupt REVLIMID treatment Resume REVLIMID at next lower dose. Do not dose below 2.5 mg daily

REVLIMID Maintenance Therapy Following Auto-HSCT

Following auto-HSCT, initiate REVLIMID maintenance therapy after adequate hematologic recovery (ANC ≥ 1000/mcL and/or platelet counts ≥75,000/mcL). The recommended starting dose of REVLIMID is 10 mg once daily continuously (Days 1-28 of repeated 28-day cycles) until disease progression or unacceptable toxicity. After 3 cycles of maintenance therapy, the dose can be increased to 15 mg once daily if tolerated.

Dose Adjustments for Hematologic Toxicities During MM Treatment

Dose modification guidelines, as summarized in Table 2 below, are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicity judged to be related to REVLIMID.

Table 2: Dose Adjustments for Hematologic Toxicities for MM

Platelet counts

Thrombocytopenia in MM

When Platelets	Recommended Course
Fall to <30,000/mcL Return to ≥30,000/mcL	Interrupt REVLIMID treatment, follow CBC weekly Resume REVLIMID at next lower dose, continuously for Days 1-28 of repeated 28-day cycle
If at the 5 mg daily dose, For a subsequent drop <30,000/mcL Return to ≥30,000/mcL	Interrupt REVLIMID treatment. Do not dose below 5 mg daily for Day 1 to 21 of 28 day cycle Resume REVLIMID at 5 mg daily for Days 1 to 21of 28-day cycle. Do not dose below 5 mg daily for Day 1 to 21 of 28 day cycle

Absolute Neutrophil counts (ANC)

Neutropenia in MM

When Neutrophils	Recommended Course
Fall to <500/mcL Return to ≥500/mcL	Interrupt REVLIMID treatment, follow CBC weekly Resume REVLIMID at next lower dose, continuously for Days 1-28 of repeated 28-day cycle
If at 5 mg daily dose, For a subsequent drop <500/mcL Return to >500/mcL	Interrupt REVLIMID treatment. Do not dose below 5 mg daily for Days 1 to 21 of 28-day cycle Resume REVLIMID at 5 mg daily for Days 1 to 21 of 28-day cycle. Do not dose below 5 mg daily for Days 1 to 21 of 28-day cycle

Other Toxicities in MM

For other Grade 3/4 toxicities judged to be related to REVLIMID, hold treatment and restart at the physician's discretion at next lower dose level when toxicity has resolved to ≤ Grade 2.

Starting Dose Adjustment for Renal Impairment in MM
[see Dosage and Administration (2.4)]

2.2 Myelodysplastic Syndromes

The recommended starting dose of REVLIMID is 10 mg daily. Treatment is continued or modified based upon clinical and laboratory findings.

Dose Adjustments for Hematologic Toxicities During MDS Treatment

Patients who are dosed initially at 10 mg and who experience thrombocytopenia should have their dosage adjusted as follows:

Platelet counts

If thrombocytopenia develops WITHIN 4 weeks of starting treatment at 10 mg daily in MDS

If baseline ≥100,000/mcL	
When Platelets	**Recommended Course**
Fall to <50,000/mcL	Interrupt REVLIMID treatment
Return to ≥50,000/mcL	Resume REVLIMID at 5 mg daily
If baseline <100,000/mcL	
When Platelets	**Recommended Course**
Fall to 50% of the baseline value	Interrupt REVLIMID treatment
If baseline ≥60,000/mcL and returns to ≥50,000/mcL	Resume REVLIMID at 5 mg daily
If baseline <60,000/mcL and returns to ≥30,000/mcL	Resume REVLIMID at 5 mg daily

If thrombocytopenia develops AFTER 4 weeks of starting treatment at 10 mg daily in MDS

When Platelets	**Recommended Course**
<30,000/mcL or <50,000/mcL with platelet transfusions	Interrupt REVLIMID treatment
Return to ≥30,000/mcL (without hemostatic failure)	Resume REVLIMID at 5 mg daily

Patients who experience thrombocytopenia at 5 mg daily should have their dosage adjusted as follows:

If thrombocytopenia develops during treatment at 5 mg daily in MDS

When Platelets	**Recommended Course**
<30,000/mcL or <50,000/mcL with platelet transfusions	Interrupt REVLIMID treatment
Return to ≥30,000/mcL (without hemostatic failure)	Resume REVLIMID at 2.5 mg daily

Patients who are dosed initially at 10 mg and experience neutropenia should have their dosage adjusted as follows:

Absolute Neutrophil counts (ANC)

If neutropenia develops WITHIN 4 weeks of starting treatment at 10 mg daily in MDS

If baseline ANC ≥1,000/mcL	
When Neutrophils	**Recommended Course**
Fall to <750/mcL	Interrupt REVLIMID treatment
Return to ≥1,000/mcL	Resume REVLIMID at 5 mg daily
If baseline ANC <1,000/mcL	
When Neutrophils	**Recommended Course**
Fall to <500/mcL	Interrupt REVLIMID treatment
Return to ≥500/mcL	Resume REVLIMID at 5 mg daily

If neutropenia develops AFTER 4 weeks of starting treatment at 10 mg daily in MDS

When Neutrophils	**Recommended Course**
<500/mcL for ≥7 days or <500/mcL associated with fever (≥38.5°C)	Interrupt REVLIMID treatment
Return to ≥500/mcL	Resume REVLIMID at 5 mg daily

Patients who experience neutropenia at 5 mg daily should have their dosage adjusted as follows:

If neutropenia develops during treatment at 5 mg daily in MDS

When Neutrophils	**Recommended Course**
<500/mcL for ≥7 days or <500/mcL associated with fever (≥38.5°C)	Interrupt REVLIMID treatment
Return to ≥500/mcL	Resume REVLIMID at 2.5 mg daily

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