

## 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 US Approval: 2005

### WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS 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 (5.2).

REVLIMID is available only through a restricted distribution program called the REVLIMID REMS™ program (formerly known as the “RevAssist® 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 THROMBOEMBOLISM

- Significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with multiple myeloma receiving REVLIMID with dexamethasone (5.4).

## RECENT MAJOR CHANGES

|  |       |
|--|-------|
| Boxed Warning                            | 02/13 |
| Contraindications (4)                    | 02/13 |
| Warnings and Precautions (5.1, 5.2, 5.9) | 02/13 |

## INDICATIONS AND USAGE

REVLIMID is a thalidomide analogue indicated for the treatment of:

- Multiple myeloma (MM), in combination with dexamethasone, in patients who have received at least one prior therapy (1.1).
- Patients with 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).

## DOSAGE AND ADMINISTRATION

- MM: 25 mg once daily orally on Days 1-21 of repeated 28-day cycles. Recommended dose of dexamethasone is 40 mg once daily on Days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg/day orally on Days 1-4 every 28 days (2.1).
- MDS: 10 mg once daily (2.2).
- Continue or modify dosing based on clinical and laboratory findings (2.1, 2.2).
- Renal impairment: Adjust starting dose in patients with moderate or severe renal impairment and on dialysis (CL<sub>cr</sub><60 mL/min) (2.1, 2.2).

## DOSAGE FORMS AND STRENGTHS

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

## CONTRAINDICATIONS

- **Pregnancy** (Boxed Warnings, 4.1, 5.1, 8.1).
- Demonstrated hypersensitivity to lenalidomide (4.2, 5.5).

## WARNINGS AND PRECAUTIONS

- Allergic Reactions, including fatalities: Hypersensitivity, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis; discontinue REVLIMID if reactions are suspected. Do not resume REVLIMID if these reactions are verified. (5.5).
- Tumor lysis syndrome (TLS) including fatalities: Monitor patients at risk of TLS (i.e., those with high tumor burden) and take appropriate precautions (5.6).
- Tumor flare reaction: Serious tumor flare reactions have occurred during investigational use of REVLIMID for chronic lymphocytic leukemia and lymphoma (5.7).
- Second Primary Malignancies (SPM): Higher incidences of SPM were observed in controlled trials of patients with multiple myeloma receiving REVLIMID (5.9)

## ADVERSE REACTIONS

- MM: Most common adverse reactions (≥20%) include fatigue, neutropenia, constipation, diarrhea, muscle cramp, anemia, pyrexia, peripheral edema, nausea, back pain, upper respiratory tract infection, dyspnea, dizziness, thrombocytopenia, tremor and rash (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 (6.2)

To report SUSPECTED ADVERSE REACTIONS or embryo-fetal exposure: contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-332-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

## DRUG INTERACTIONS

- Digoxin: Periodic monitoring of digoxin plasma levels is recommended due to increased C<sub>max</sub> 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 venous thromboembolism (VTE) (7.3)

## USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Discontinue drug or nursing taking into consideration importance of drug to the mother. (8.3)
- Patients with Renal Insufficiency: Adjust the starting dose of with moderate or severe renal impairment and on dialysis (2.1, 2.2).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 02/2013

---

**FULL PRESCRIBING INFORMATION CONTENTS\***  
**WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS THROMBOEMBOLISM**

**1 INDICATIONS AND USAGE**

- 1.1 Multiple Myeloma
- 1.2 Myelodysplastic Syndromes

**2 DOSAGE AND ADMINISTRATION**

- 2.1 Multiple Myeloma
- 2.2 Myelodysplastic Syndromes

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

- 4.1 Pregnancy
- 4.2 Allergic Reactions

**5 WARNINGS AND PRECAUTIONS**

- 5.1 Embryo-Fetal Toxicity
- 5.2 REVLIMID REMS™ program
- 5.3 Hematologic Toxicity
- 5.4 Venous Thromboembolism
- 5.5 Allergic Reactions
- 5.6 Tumor Lysis Syndrome
- 5.7 Tumor Flare Reaction
- 5.8 Hepatotoxicity
- 5.9 Second Primary Malignancies

**6 ADVERSE REACTIONS**

- 6.1 Clinical Trials Experience in Multiple Myeloma
- 6.2 Clinical Trials Experience in Myelodysplastic Syndromes
- 6.3 Postmarketing Experience

**7 DRUG INTERACTIONS**

- 7.1 Digoxin
- 7.2 Warfarin
- 7.3 Concomitant Therapies That May Increase the Risk of Thrombosis

**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy

- 8.3 Nursing mothers
- 8.4 Pediatric use
- 8.5 Geriatric use
- 8.6 Females of Reproductive Potential and Males
- 8.7 Renal Impairment
- 8.8 Hepatic Impairment

**10 OVERDOSAGE**

**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

**13 NONCLINICAL TOXICOLOGY**

- 13.1 Carcinogenesis, mutagenesis, impairment of fertility

**14 CLINICAL STUDIES**

- 14.1 Multiple Myeloma
- 14.2 Myelodysplastic Syndromes (MDS) with a Deletion 5q Cytogenetic Abnormality

**15 REFERENCES**

**16 HOW SUPPLIED/STORAGE AND HANDLING**

- 16.1 How Supplied
- 16.2 Storage
- 16.3 Handling and Disposal

**17 PATIENT COUNSELING INFORMATION**

\*Sections or subsections omitted from the Full Prescribing Information are not listed

## FULL PRESCRIBING INFORMATION

### WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS 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<sup>®</sup> 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<sup>™</sup> program (formerly known as the “RevAssist<sup>®</sup>” program) (5.2).

Information about the REVLIMID REMS<sup>™</sup> 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 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 Thromboembolism

REVLIMID has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with multiple myeloma who were treated with REVLIMID and dexamethasone therapy. Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with REVLIMID may lessen the potential for venous thromboembolism. The decision to take prophylactic measures should be done carefully after an assessment of an individual patient’s underlying risk factors

## 1 INDICATIONS AND USAGE

### 1.1 Multiple Myeloma

REVLIMID in combination with dexamethasone is indicated for the treatment of patients with multiple myeloma (MM) who have received at least one prior therapy.

### 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.

## 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

The recommended starting dose of REVLIMID is 25 mg once daily on Days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg once daily on Days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily orally on Days 1-4 every 28 days. Treatment is continued or modified based upon clinical and laboratory findings.

#### **Dose Adjustments for Hematologic Toxicities During Multiple Myeloma Treatment**

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

#### **Platelet counts**

##### **Thrombocytopenia in MM**

| <b>When Platelets</b>                | <b>Recommended Course</b>   |
|--------------------------------------|---|
| Fall to <30,000/mcL                  | Interrupt REVLIMID treatment, follow CBC weekly                                   |
| Return to ≥30,000/mcL                | Restart REVLIMID at 15 mg daily   |
| For each subsequent drop <30,000/mcL | Interrupt REVLIMID treatment  |
| Return to ≥30,000/mcL                | Resume REVLIMID at 5 mg less than the previous dose. Do not dose below 5 mg daily |

**Absolute Neutrophil counts (ANC)**

**Neutropenia in MM**

| <b>When Neutrophils</b>  | <b>Recommended Course</b>   |
|--|---|
| Fall to <1000/mcL  | Interrupt REVLIMID treatment, add G-CSF, follow CBC weekly                        |
| Return to $\geq 1,000$ /mcL and neutropenia is the only toxicity | Resume REVLIMID at 25 mg daily  |
| Return to $\geq 1,000$ /mcL and if other toxicity                | Resume REVLIMID at 15 mg daily  |
| For each subsequent drop <1,000/mcL                              | Interrupt REVLIMID treatment  |
| Return to $\geq 1,000$ /mcL                                      | Resume REVLIMID at 5 mg less than the previous dose. Do not dose below 5 mg daily |

**Other Grade 3 / 4 Toxicities in MM**

For other Grade 3/4 toxicities judged to be related to REVLIMID, hold treatment and restart at next lower dose level when toxicity has resolved to  $\leq$  Grade 2.

**Starting Dose Adjustment for Renal Impairment in MM**

Since REVLIMID is primarily excreted unchanged by the kidney, adjustments to the starting dose of REVLIMID are recommended to provide appropriate drug exposure in patients with moderate or severe renal impairment and in patients on dialysis. Based on a pharmacokinetic study in patients with renal impairment due to nonmalignant conditions, REVLIMID starting dose adjustment is recommended for patients with CLcr < 60 mL/min. Non-dialysis patients with creatinine clearances less than 11 mL/min and dialysis patients with creatinine clearances less than 7 mL/min have not been studied. The recommendations for initial starting doses for patients with multiple myeloma (MM) are as follows:

**Table 1: Starting Dose Adjustment for Renal Impairment in Multiple Myeloma (Days 1 – 21 of each 28 day cycle)**

| <b>Category</b>                  | <b>Renal Function (Cockcroft-Gault)</b>   | <b>Dose</b>   |
|----------------------------------|---|---|
| <b>Moderate Renal Impairment</b> | CLcr 30-60 mL/min                         | 10 mg<br>Every 24 hours   |
| <b>Severe Renal Impairment</b>   | CLcr < 30 mL/min (not requiring dialysis) | 15 mg<br>Every 48 hours   |
| <b>End Stage Renal Disease</b>   | CLcr < 30 mL/min (requiring dialysis)     | 5 mg<br>Once daily. On dialysis days, administer the dose following dialysis. |

After initiation of REVLIMID therapy, subsequent REVLIMID dose modification should be based on individual patient treatment tolerance, as described elsewhere in this section.

**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**

| <b>If baseline <math>\geq 100,000</math>/mcL</b>                 |                               |
|--|-------------------------------|
| <b>When Platelets</b>  | <b>Recommended Course</b>     |
| Fall to <50,000/mcL  | Interrupt REVLIMID treatment  |
| Return to $\geq 50,000$ /mcL                                     | Resume REVLIMID at 5 mg daily |
| <b>If baseline &lt;100,000/mcL</b>                               |                               |
| <b>When Platelets</b>  | <b>Recommended Course</b>     |
| Fall to 50% of the baseline value                                | Interrupt REVLIMID treatment  |
| If baseline $\geq 60,000$ /mcL and returns to $\geq 50,000$ /mcL | Resume REVLIMID at 5 mg daily |
| If baseline <60,000/mcL and returns to $\geq 30,000$ /mcL        | Resume REVLIMID at 5 mg daily |

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

| <b>When Platelets</b>      | <b>Recommended Course</b>    |
|----------------------------|------------------------------|
| <30,000/mcL or <50,000/mcL | Interrupt REVLIMID treatment |

|  |                               |
|--|-------------------------------|
| with platelet transfusions<br>Return to $\geq 30,000/\text{mcL}$<br>(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  |
|--|---|
| $< 30,000/\text{mcL}$ or $< 50,000/\text{mcL}$<br>with platelet transfusions<br>Return to $\geq 30,000/\text{mcL}$<br>(without hemostatic failure) | Interrupt REVLIMID treatment<br><br>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**

| When Neutrophils  | Recommended Course  |
|---|---|
| Fall to $< 750/\text{mcL}$<br>Return to $\geq 1,000/\text{mcL}$ | Interrupt REVLIMID treatment<br>Resume REVLIMID at 5 mg daily |
| <b>If baseline ANC <math>&lt; 1,000/\text{mcL}</math></b>       |   |
| When Neutrophils  | Recommended Course  |
| Fall to $< 500/\text{mcL}$<br>Return to $\geq 500/\text{mcL}$   | Interrupt REVLIMID treatment<br>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  |
|--|---|
| $< 500/\text{mcL}$ for $\geq 7$ days or $< 500/\text{mcL}$<br>associated with fever ( $\geq 38.5^\circ\text{C}$ )<br>Return to $\geq 500/\text{mcL}$ | Interrupt REVLIMID treatment<br><br>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  |
|--|---|
| $< 500/\text{mcL}$ for $\geq 7$ days or $< 500/\text{mcL}$<br>associated with fever ( $\geq 38.5^\circ\text{C}$ )<br>Return to $\geq 500/\text{mcL}$ | Interrupt REVLIMID treatment<br><br>Resume REVLIMID at 2.5 mg daily |

**Other Grade 3 / 4 Toxicities in MDS**

For other Grade 3/4 toxicities judged to be related to REVLIMID, hold treatment and restart at next lower dose level when toxicity has resolved to  $\leq$  Grade 2.

**Starting Dose Adjustment for Renal Impairment in MDS:**

Since REVLIMID is primarily excreted unchanged by the kidney, adjustments to the starting dose of REVLIMID are recommended to provide appropriate drug exposure in patients with moderate or severe renal impairment and in patients on dialysis. Based on a pharmacokinetic study in patients with renal impairment due to nonmalignant conditions, REVLIMID starting dose adjustment is recommended for patients with  $\text{CL}_{\text{Cr}} < 60$  mL/min. Non-dialysis patients with creatinine clearances less than 11 mL/min and dialysis patients with creatinine clearances less than 7 mL/min have not been studied. The recommendations for initial starting doses for patients with myelodysplastic syndromes (MDS) are as follows:

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.