REVLIMID® (lenalidomide)

2.5 mg, 5 mg, 10 mg, 15 mg and 25 mg capsules

CREVPI11

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
Initial U.S. Approval: 2005

WARNING: FETAL RISK, HEMATOLOGIC TOXICITY, and DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM
See full prescribing information for complete boxed warning.

Fetal Risk

- **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 death to a developing baby.**
- **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 under a restricted distribution program called "RevAssist." (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).

Deep Vein Thrombosis and Pulmonary Embolism

- **Significantly increased risk of DVT and PE in patients with multiple myeloma receiving REVLIMID with dexamethasone (5.4).**

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

Dosage and Administration (2, 2.1, 2.2)	06/10
Dosage Forms and Strengths (3)	06/10
Warnings and Precautions (5.2, 5.5, 5.8)	06/10
Adverse Reactions – Postmarketing Experience (6.3)	06/10
Drug Interactions (7, 7.1, 7.2)	06/10
Use in Special Populations (8.6)	06/10
Overdosage (10)	06/10
Description (11)	06/10
Clinical Pharmacology (12.3)	06/10
How Supplied/Storage and Handling (16)	06/10
Patient Counseling Information (17.4, 17.5)	06/10

----------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 (CLcr<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----------

- Females of childbearing potential: Must have 2 negative pregnancy tests before starting treatment with REVLIMID and must use two forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after treatment. Reproductive Risk and Special Prescribing Requirements: To avoid fetal exposure REVLIMID is only available under a special restricted distribution program called RevAssist (Boxed Warnings, 4.1, 5.1, 17).
- Hematologic Toxicity: This drug is associated with significant neutropenia and thrombocytopenia. Patients may require dose interruption and/or dose reduction (5.3, 6.1).
- Deep vein thrombosis and pulmonary embolism: Physicians and patients should be observant for signs and symptoms of thromboembolism (5.4, 6.1).
- Allergic Reactions: include hypersensitivity, angioedema, Stevens-Johnson syndrome, and toxic epidermal necrolysis. In some cases these allergic reactions may be fatal. Discontinue REVLIMID if any such reactions are suspected. Revlimid should not be resumed following discontinuation for these reactions. REVLIMID capsules contain lactose. Risk-benefit of REVLIMID treatment should be evaluated in patients with lactose intolerance (5.5).
- Tumor lysis syndrome (TLS): Fatal instances of TLS have been reported during treatment with lenalidomide. 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).

----------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; contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-332-1088 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 venous thromboembolic events (VTE). (7.3)

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

- Patients with Renal Insufficiency: Adjustment of the starting dose of REVLIMID is recommended in patients with moderate or severe renal impairment and in patients on dialysis (2.1, 2.2).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: April 2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: FETAL RISK, HEMATOLOGIC TOXICITY, and DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM

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 death to a developing baby. In women of childbearing potential, obtain 2 negative pregnancy tests before starting REVLIMID® treatment. Women of childbearing 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 fetal exposure to lenalidomide, REVLIMID is only available under a restricted distribution program called "RevAssist®" (5.2).

Information about the RevAssist program is available at www.REVLIMID.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)]*.

Deep Vein Thrombosis and Pulmonary Embolism

REVLIMID has demonstrated an 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 thromboembolic events. The decision to take prophylactic measures should be done carefully after an assessment of an individual patient's underlying risk factors.

FULL PRESCRIBING INFORMATION

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

When Platelets	Recommended Course
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

When Neutrophils	Recommended Course
Fall to <1000/mcL	Interrupt REVLIMID treatment, add G-CSF, follow CBC weekly
Return to ≥1,000/mcL and neutropenia is the only toxicity	Resume REVLIMID at 25 mg daily
Return to ≥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 ≥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 ≤ Grade 2.

Starting Dose Adjustment for Renal Impairment in MM

Since REVLIMD 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)

Category	Renal Function (Cockcroft-Gault)	Dose
Moderate Renal Impairment	CLcr 30-60 mL/min	10 mg Every 24 hours
Severe Renal Impairment	CLcr < 30 mL/min (not requiring dialysis)	15 mg Every 48 hours
End Stage Renal Disease	CLcr < 30 mL/min (requiring dialysis)	5 mg 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

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

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 ≤ 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 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 myelodysplastic syndromes (MDS) are as follows:

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