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 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 (5.2).**

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 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----------

Boxed Warning	09/14
Indication and Usage (1.4)	11/13
Warnings and Precautions (5.4)	09/14
Warnings and Precautions (5.5, 5.10)	11/13

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

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

- Multiple myeloma (MM), in combination with dexamethasone, in patients who have received at least one prior therapy (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: 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).
- 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).
- Renal impairment: Adjust starting dose in patients with moderate or severe renal impairment and on dialysis (CLcr<60 mL/min) (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 hypersensitivity to lenalidomide (4.2, 5.5).

----------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 multiple myeloma receiving REVLIMID (5.6).
- Hepatotoxicity: Hepatic failure including fatalities; monitor liver function. Stop REVLIMID and evaluate if hepatotoxicity is suspected (5.7).
- 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 (5.8).
- Tumor lysis syndrome (TLS) including fatalities: Monitor patients at risk of TLS (i.e., those with high tumor burden) and take appropriate precautions (5.9).
- Tumor flare reaction: Serious tumor flare reactions have occurred during investigational use of REVLIMID for chronic lymphocytic leukemia and lymphoma (5.10, 6.3).

----------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).
- MCL: Most common adverse reactions (≥15%) include neutropenia, thrombocytopenia, fatigue, diarrhea, anemia, nausea, cough, pyrexia, rash, dyspnea, pruritus, constipation, peripheral edema and leukopenia (6.3).

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 (7.3).

----------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 (2.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 09/2014

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 (formerly known as the "RevAssist®" 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) 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.

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

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 REVLIMID.

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 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 Section 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

Other Grade 3 / 4 Toxicities in MDS

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 MDS:

See Section 2.4.

2.3 Mantle Cell Lymphoma

The recommended starting dose of REVLIMID is 25 mg/day orally on Days 1-21 of repeated 28-day cycles for relapsed or refractory mantle cell lymphoma. Treatment should be continued until disease progression or unacceptable toxicity.

Treatment is continued, modified or discontinued based upon clinical and laboratory findings.

Dose Adjustments for Hematologic Toxicities During MCL Treatment

Dose modification guidelines as summarized below are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicities considered to be related to REVLIMID.

Platelet counts

Thrombocytopenia during treatment in MCL

When Platelets	**Recommended Course**
Fall to <50,000/mcL	Interrupt REVLIMID treatment and follow CBC weekly
Return to ≥50,000/mcL	Resume REVLIMID at 5 mg less than the previous dose. Do not dose below 5 mg daily

Absolute Neutrophil counts (ANC)

Neutropenia during treatment in MCL

When Neutrophils	**Recommended Course**

Fall to <1000/mcL for at least 7 days OR Falls to < 1,000/mcL with an associated temperature ≥ 38.5°C OR Falls to < 500 /mcL	Interrupt REVLIMID treatment and follow CBC weekly
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 MCL

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 MCL:

See Section 2.4.

2.4 Starting Dose for Renal Impairment in MM, MDS or MCL

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 non-malignant 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 MM, MDS or MCL are as follows:

Table 1: Starting Dose Adjustments for Patients with Renal Impairment in MM, MDS or MCL

Category	Renal Function (Cockcroft-Gault)	Dose in MM or MCL	Dose in MDS
Moderate Renal Impairment	CLcr 30-60 mL/min	10 mg Every 24 hours	5 mg Every 24 hours
Severe Renal Impairment	CLcr < 30 mL/min (not requiring dialysis)	15 mg Every 48 hours	2.5 mg Every 24 hours
End Stage Renal Disease	CLcr < 30 mL/min (requiring dialysis)	5 mg Once daily. On dialysis days, administer the dose following dialysis.	2.5 mg Once daily. On dialysis days, administer the dose following dialysis.

After initiation of REVLIMID therapy, subsequent REVLIMID dose modification is based on individual patient treatment tolerance, as described elsewhere (see section 2).

3 DOSAGE FORMS AND STRENGTHS

REVLIMID 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg and 25 mg capsules will be supplied through the REVLIMID REMS™ program.

REVLIMID is available in the following capsule strengths:

2.5 mg: White and blue-green opaque hard capsules imprinted "REV" on one half and "2.5 mg" on the other half in black ink
5 mg: White opaque capsules imprinted "REV" on one half and "5 mg" on the other half in black ink
10 mg: Blue/green and pale yellow opaque capsules imprinted "REV" on one half and "10 mg" on the other half in black ink
15 mg: Powder blue and white opaque capsules imprinted "REV" on one half and "15 mg" on the other half in black ink
20 mg: Powder blue and blue-green opaque hard capsules imprinted "REV" on one half and "20 mg" on the other half in black ink
25 mg: White opaque capsules imprinted "REV" on one half and "25 mg" on the other half in black ink

4 CONTRAINDICATIONS

4.1 Pregnancy

REVLIMID can cause fetal harm when administered to a pregnant female. Limb abnormalities were seen in the offspring of monkeys that were dosed with lenalidomide during organogenesis. This effect was seen at all doses tested. Due to the results of this developmental monkey study, and lenalidomide's structural similarities to thalidomide, a known human teratogen, lenalidomide is contraindicated in females who are pregnant [*see Boxed Warning*]. 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 hazard to the fetus [*see Warnings and Precautions (5.1, 5.2), Use in Special Populations (8.1), (8.6)*].

4.2 Allergic Reactions

REVLIMID is contraindicated in patients who have demonstrated hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide [*see Warnings and Precautions (5.5)*].

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

REVLIMID is a thalidomide analogue and is contraindicated for use during pregnancy. Thalidomide is a known human teratogen that causes life-threatening human birth defects or embryo-fetal death [*see Use in Specific Populations (8.1)*]. An embryo-fetal development study in monkeys indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy, similar to birth defects observed in humans following exposure to thalidomide during pregnancy.

REVLIMID is only available through the REVLIMID REMS™ program (formerly known as the "RevAssist® program") [*see Warnings and Precautions (5.2)*].

Females of Reproductive Potential
Females of reproductive potential must avoid pregnancy for at least 4 weeks before beginning REVLIMID therapy, during therapy, during dose interruptions and for at least 4 weeks after completing therapy.

Females must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control, beginning 4 weeks prior to initiating treatment with REVLIMID, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of REVLIMID therapy.

Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing REVLIMID therapy and then weekly during the first month, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles [*see Use in Specific Populations (8.6)*].

Males
Lenalidomide is present in the semen of patients receiving the drug. Therefore, 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 28 days after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm [*see Use in Specific Populations (8.6)*].

Blood Donation
Patients must not donate blood during treatment with REVLIMID and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to REVLIMID.

5.2 REVLIMID REMS™ program

Because of the embryo-fetal risk [*see Warnings and Precautions (5.1)*], REVLIMID is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS), the **REVLIMID REMS™** program **(formerly known as the "RevAssist®" program).**

Required components of the **REVLIMID REMS™** program include the following:

- Prescribers must be certified with the **REVLIMID REMS™** program by enrolling and complying with the REMS requirements.
- Patients must sign a Patient-Physician agreement form and comply with the REMS requirements. In particular, female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements [see *Use in Specific Populations (8.6)*] and males must comply with contraception requirements [*see Use in Specific Populations (8.6)*].
- Pharmacies must be certified with the **REVLIMID REMS™** program, must only dispense to patients who are authorized to receive REVLIMID and comply with REMS requirements.

Further information about the **REVLIMID REMS™** program is available at www.celgeneriskmanagement.com or by telephone at 1-888-423-5436.

5.3 Hematologic Toxicity

REVLIMID can cause significant neutropenia and thrombocytopenia. Patients taking REVLIMID for MDS should have their complete blood counts monitored weekly for the first 8 weeks and at least monthly thereafter. Patients taking REVLIMID for MM should have their complete blood counts monitored every 2 weeks for the first 12 weeks and then monthly thereafter. Patients taking REVLIMID for MCL should have their complete blood counts monitored weekly for the first cycle (28 days), every 2 weeks during cycles 2-4, and then monthly thereafter. Patients may require dose interruption and/or dose reduction [*see Dosage and Administration (2.1,* 2.2, 2.3*)*].

Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the MDS study. In the 48% of patients who developed Grade 3 or 4 neutropenia, the median time to onset was 42 days (range, 14-411 days), and the median time to documented recovery was 17 days (range, 2-170 days). In the 54% of patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was 28 days (range, 8-290 days), and the median time to documented recovery was 22 days (range, 5-224 days [*see Boxed Warning and Dosage and Administration (2.2)*].

In the pooled MM trials Grade 3 and 4 hematologic toxicities were more frequent in patients treated with the combination of REVLIMID and dexamethasone than in patients treated with dexamethasone alone [*see Adverse Reactions (6.1)*].

In the MCL trial, Grade 3 or 4 neutropenia was reported in 43% of the patients. Grade 3 or 4 thrombocytopenia was reported in 28% of the patients.

5.4 Venous and Arterial Thromboembolism

Venous thromboembolic events (deep venous thrombosis and pulmonary embolism) and arterial thromboses are increased in patients treated with REVLIMID. A significantly increased risk of DVT (7.4%) and of PE (3.7%) occurred in patients with multiple myeloma who were treated with

REVLIMID and dexamethasone therapy compared to patients treated in the placebo and dexamethasone group (3.1% and 0.9%) in clinical trials with varying use of anticoagulant therapies [*see Boxed Warning and Adverse Reactions (6.1)*].

Myocardial infarction (1.7%) and stroke (CVA) (2.3%) are increased in patients with multiple myeloma who were treated with REVLIMID and dexamethasone therapy compared to patients treated with placebo and dexamethasone (0.6%, and 0.9%) in clinical trials [*see Adverse Reactions (6.1)*]. 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)

In controlled clinical trials that did not use concomitant thromboprophylaxis, 21.5% overall thrombotic events (Standardized MedDRA Query Embolic and Thrombotic events) occurred in patients with refractory and relapsed multiple myeloma who were treated with REVLIMID and dexamethasone compared to 8.3% thrombosis in patients treated with placebo and dexamethasone The median time to first thrombosis event was 2.7 months. Thromboprophylaxis is recommended. The regimen of thromboprophylaxis should be based on an assessment of the patient's underlying risks. Instruct patients to report immediately any signs and symptoms suggestive of thrombotic events. ESAs and estrogens may further increase the risk of thrombosis and their use should be based on a benefit-risk decision in patients receiving REVLIMID [*see Drug Interactions (7.3*)].

5.5 Increased Mortality in Patients with CLL

In a prospective randomized (1:1) clinical trial in the first line treatment of patients with chronic lymphocytic leukemia, single agent REVLIMID therapy increased the risk of death as compared to single agent chlorambucil. In an interim analysis, there were 34 deaths among 210 patients on the REVLIMID treatment arm compared to 18 deaths among 211 patients in the chlorambucil treatment arm, and hazard ratio for overall survival was 1.92 [95% CI: 1.08 – 3.41], consistent with a 92% increase in the risk of death. The trial was halted for safety in July 2013.

Serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure occurred more frequently in the REVLIMID treatment arm. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials.

5.6 Second Primary Malignancies

Patients with multiple myeloma treated with lenalidomide in studies including melphalan and stem cell transplantation had a higher incidence of second primary malignancies, particularly acute myelogenous leukemia (AML) and Hodgkin lymphoma, compared to patients in the control arms who received similar therapy but did not receive lenalidomide. Monitor patients for the development of second malignancies. Take into account both the potential benefit of lenalidomide and the risk of second primary malignancies when considering treatment with lenalidomide.

5.7 Hepatotoxicity

Hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dexamethasone. In clinical trials, 15% of patients experienced hepatotoxicity (with hepatocellular, cholestatic and mixed characteristics); 2% of patients with multiple myeloma and 1% of patients with myelodysplasia had serious hepatotoxicity events. The mechanism of drug-induced hepatotoxicity is unknown. 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.

5.8 Allergic Reactions

Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) 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. REVLIMID interruption or discontinuation should be considered for Grade 2-3 skin rash. REVLIMID must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected and 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**.**

5.9 Tumor Lysis Syndrome

Fatal instances of tumor lysis syndrome have been reported during treatment with lenalidomide. The patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

5.10 Tumor Flare Reaction

Tumor flare reaction has occurred during investigational use of lenalidomide for CLL and lymphoma, and is characterized by tender lymph node swelling, low grade fever, pain and rash. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials.

Monitoring and evaluation for tumor flare reaction (TFR) is recommended in patients with MCL. Tumor flare reaction may mimic progression of disease (PD). In the MCL trial, 13/134 (10%) of subjects experienced TFR; all reports were Grade 1 or 2 in severity. All of the events occurred in cycle 1 and one patient developed TFR again in cycle 11. Lenalidomide may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician's discretion. Patients with Grade 1 and 2 TFR may also be treated with corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and/or narcotic analgesics for management of TFR symptoms. In patients with Grade 3 or 4 TFR, it is recommended to withhold treatment with lenalidomide until TFR resolves to ≤ Grade 1. Patients with Grade 3 or 4 TFR may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR.

6 ADVERSE REACTIONS

The following adverse reactions are described in detail in other sections of the prescribing information:

- Embryo-Fetal Toxicity [*see Boxed Warnings, Warnings and Precautions (5.1, 5.2)*]
- Neutropenia and thrombocytopenia [*see Boxed Warnings, Warnings and Precautions (5.3)*]
- Venous and arterial thromboembolism [*see Boxed Warnings, Warnings and Precautions (5.4)]*
- Increased Mortality in Patients with CLL [*see Warnings and Precautions (5.5)]*
- Second Primary Malignancies [*see Warnings and Precautions (5.6)*]
- Hepatotoxicity [*see Warnings and Precautions (5.7)*]
- Allergic Reactions [*see Warnings and Precautions (5.8)*]
- Tumor lysis syndrome [*see Warnings and Precautions (5.9)*]
- Tumor flare reactions [*see Warnings and Precautions (5.10)*]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience in Multiple Myeloma

Data were evaluated from 703 patients in two studies who received at least one dose of REVLIMID/dexamethasone (353 patients) or placebo/dexamethasone (350 patients).

In the REVLIMID/dexamethasone treatment group, 269 patients (76%) had at least one dose interruption with or without a dose reduction of REVLIMID compared to 199 patients (57%) in the placebo/dexamethasone treatment group. Of these patients who had one dose interruption with or without a dose reduction, 50% in the REVLIMID/dexamethasone treatment group had at least one additional dose interruption with or without a dose reduction compared to 21% in the placebo/dexamethasone treatment group. Most adverse events and Grade 3/4 adverse events were more frequent in patients who received the combination of REVLIMID/dexamethasone compared to placebo/dexamethasone.

Tables 2, 3, and 4 summarize the adverse reactions reported for REVLIMID/dexamethasone and placebo/dexamethasone groups.

Table 2: Adverse Reactions Reported in ≥5% of Patients and with a ≥2% Difference in Proportion of Patients Between the REVLIMID/dexamethasone and Placebo/dexamethasone Groups

System Organ Class/ Preferred Term	REVLIMID/Dex* (n=353) n (%)	Placebo/Dex * (n=350) n (%)
Blood and lymphatic system disorders		
Neutropenia [%]	149 (42.2)	22 (6.3)
Anemia [@]	111 (31.4)	83 (23.7)
Thrombocytopenia [@]	76 (21.5)	37 (10.6)
Leukopenia	28 (7.9)	4 (1.1)
Lymphopenia	19 (5.4)	5 (1.4)
General disorders and administration site conditions		
Fatigue	155 (43.9)	146 (41.7)
Pyrexia	97 (27.5)	82 (23.4)
Peripheral edema	93 (26.3)	74 (21.1)
Chest Pain	29 (8.2)	20 (5.7)
Lethargy	24 (6.8)	8 (2.3)
Gastrointestinal disorders		
Constipation	143 (40.5)	74 (21.1)
Diarrhea[@]	136 (38.5)	96 (27.4)
Nausea [@]	92 (26.1)	75 (21.4)
Vomiting [@]	43 (12.2)	33 (9.4)
Abdominal Pain [@]	35 (9.9)	22 (6.3)
Dry Mouth	25 (7.1)	13 (3.7)
Musculoskeletal and connective tissue disorders		
Muscle cramp	118 (33.4)	74 (21.1)
Back pain	91 (25.8)	65 (18.6)
Bone Pain	48 (13.6)	39 (11.1)
Pain in Limb	42 (11.9)	32 (9.1)
Nervous system disorders		
Dizziness	82 (23.2)	59 (16.9)

System Organ Class/ Preferred Term	REVLIMID/Dex* (n=353) n (%)	Placebo/Dex * (n=350) n (%)
Tremor	75 (21.2)	26 (7.4)
Dysgeusia	54 (15.3)	34 (9.7)
Hypoaesthesia	36 (10.2)	25 (7.1)
Neuropathy [a]	23 (6.5)	13 (3.7)
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	83 (23.5)	60 (17.1)
Nasopharyngitis	62 (17.6)	31 (8.9)
Pharyngitis	48 (13.6)	33 (9.4)
Bronchitis	40 (11.3)	30 (8.6)
Infections[b] and infestations		
Upper respiratory tract infection	87 (24.6)	55 (15.7)
Pneumonia [@]	48 (13.6)	29 (8.3)
Urinary Tract Infection	30 (8.5)	19 (5.4)
Sinusitis	26 (7.4)	16 (4.6)
Skin and subcutaneous system disorders		
Rash [c]	75 (21.2)	33 (9.4)
Sweating Increased	35 (9.9)	25 (7.1)
Dry Skin	33 (9.3)	14 (4.0)
Pruritus	27 (7.6)	18 (5.1)
Metabolism and nutrition disorders		
Anorexia	55 (15.6)	34 (9.7)
Hypokalemia	48 (13.6)	21 (6.0)
Hypocalcemia	31 (8.8)	10 (2.9)
Appetite Decreased	24 (6.8)	14 (4.0)
Dehydration	23 (6.5)	15 (4.3)
Hypomagnesaemia	24 (6.8)	10 (2.9)
Investigations		
Weight Decreased	69 (19.5)	52 (14.9)
Eye disorders		
Blurred vision	61 (17.3)	40 (11.4)
Vascular disorders		
Deep vein thrombosis [%]	33 (9.3)	15 (4.3)
Hypertension	28 (7.9)	20 (5.7)
Hypotension	25 (7.1)	15 (4.3)

Table 3: Grade 3/4 Adverse Reactions Reported in ≥2% Patients and With a ≥1% Difference in Proportion of Patients Between the REVLIMID/dexamethasone and Placebo/dexamethasone groups

System Organ Class/ Preferred Term	REVLIMID/Dex[#] (n=353) n (%)	Placebo/Dex[#] (n=350) n (%)
Blood and lymphatic system disorders		
Neutropenia [%]	118 (33.4)	12 (3.4)
Thrombocytopenia [@]	43 (12.2)	22 (6.3)
Anemia [@]	35 (9.9)	20 (5.7)
Leukopenia	14 (4.0)	1 (0.3)
Lymphopenia	10 (2.8)	4 (1.1)
Febrile Neutropenia [%]	8 (2.3)	0 (0.0)

System Organ Class/ Preferred Term	REVLIMID/Dex[#] (n=353) n (%)	Placebo/Dex[#] (n=350) n (%)
General disorders and administration site conditions		
Fatigue	23 (6.5)	17 (4.9)
Vascular disorders		
Deep vein thrombosis [%]	29 (8.2)	12 (3.4)
Infections[b] and infestations		
Pneumonia [@]	30 (8.5)	19 (5.4)
Urinary Tract Infection	5 (1.4)	1 (0.3)
Metabolism and nutrition disorders		
Hypokalemia	17 (4.8)	5 (1.4)
Hypocalcemia	13 (3.7)	6 (1.7)
Hypophosphatemia	9 (2.5)	0 (0.0)
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism[@]	14 (4.0)	3 (0.9)
Respiratory Distress [@]	4 (1.1)	0 (0.0)
Musculoskeletal and connective tissue disorders		
Muscle weakness	20 (5.7)	10 (2.9)
Gastrointestinal disorders		
Diarrhea [@]	11 (3.1)	4 (1.1)
Constipation	7 (2.0)	1 (0.3)
Nausea [@]	6 (1.7)	2 (0.6)
Cardiac disorders		
Atrial fibrillation [@]	13 (3.7)	4 (1.1)
Tachycardia	6 (1.7)	1 (0.3)
Cardiac Failure Congestive [@]	5 (1.4)	1 (0.3)
Nervous System disorders		
Syncope	10 (2.8)	3 (0.9)
Dizziness	7 (2.0)	3 (0.9)
Eye Disorders		
Cataract	6 (1.7)	1 (0.3)
Cataract Unilateral	5 (1.4)	0 (0.0)
Psychiatric Disorder		
Depression	10 (2.8)	6 (1.7)

Table 4: Serious Adverse Reactions Reported in ≥1% Patients and With a ≥1% Difference in Proportion of Patients Between the REVLIMID/dexamethasone and Placebo/dexamethasone Groups

System Organ Class/ Preferred Term	REVLIMID/Dex[&] (n=353) n (%)	Placebo/Dex[&] (n=350) n (%)
Blood and lymphatic system disorders		
Febrile Neutropenia[%]	6 (1.7)	0 (0.0)
Vascular disorders		
Deep vein thrombosis[%]	26 (7.4)	11 (3.1)
Infections[b] and infestations		
Pneumonia [@]	33 (9.3)	21 (6.0)
Respiratory, thoracic, and mediastinal disorders		
Pulmonary embolism[@]	13 (3.7)	3 (0.9)
Cardiac disorders		

System Organ Class/ Preferred Term	REVLIMID/Dex[&] (n=353) n (%)	Placebo/Dex[&] (n=350) n (%)
Atrial fibrillation [@]	11 (3.1)	2 (0.6)
Cardiac Failure Congestive [@]	5 (1.4)	0 (0.0)
Nervous system disorders		
Cerebrovascular accident [@]	7 (2.0)	3 (0.9)
Gastrointestinal disorders		
Diarrhea [@]	6 (1.7)	2 (0.6)
Musculoskeletal and connective tissue disorders		
Bone Pain	4 (1.1)	0 (0.0)

For all tables above:
n – Number of Patients
* - All Treatment Emergent AEs with ≥5% of Patients in REVLIMID/ Dex and at Least 2% Difference in Proportion between the Two Arms - (Safety population)
# - All Treatment Emergent Grades 3 and 4 AEs with ≥1% Patients in REVLIMID/ Dex and at Least 1% Difference in Proportion between the Two Arms - (Safety population)
& - All Treatment Emergent Serious AEs with ≥1% Patients in REVLIMID/ Dex and at Least 1% Difference in Proportion between the Two Arms - (Safety population)
@ - ADRs with Death as an outcome
% - ADRs which were considered to be life threatening (if the outcome of the event was death, it is included with death cases)
[a] - All PTs under the MedDRA SMQ of Neuropathy of a peripheral sensory nature will be considered listed
[b] - All PTs under SOC of Infections except for rare infections of Public Health interest will be considered listed
[c] - All PTs under HLT of Rash will be considered listed
Dex=dexamethasone
Median duration of exposure among patients treated with REVLIMID/dexamethasone was 44 weeks while median duration of exposure among patients treated with placebo/dexamethasone was 23 weeks. This should be taken into consideration when comparing frequency of adverse events between two treatment groups REVLIMID/dexamethasone vs. placebo/dexamethasone.

Venous and Arterial Thromboembolism [*see Boxed Warning, Warnings and Precautions (5.4)*]

Deep vein thrombosis (DVT) was reported as a serious (7.4%) or severe (8.2%) adverse drug reaction at a higher rate in the REVLIMID/dexamethasone group compared to 3.1 % and 3.4% in the placebo/dexamethasone group, respectively. Discontinuations due to DVT adverse reactions were reported at comparable rates between groups.

Pulmonary embolism (PE) was reported as a serious adverse drug reaction including Grade 3/4 (3.7%) at a higher rate in the REVLIMID/dexamethasone group compared to 0.9% in the placebo/dexamethasone group. Discontinuations due to PE adverse reactions were reported at comparable rates between groups.

Myocardial infarction was reported as a serious (1.7%) or severe (1.7%) adverse drug reaction at a higher rate in the REVLIMID/dexamethasone group compared to 0.6 % and 0.6% respectively in the placebo/dexamethasone group. Discontinuation due to MI (including acute) adverse reactions was 0.8% in REVLIMID/dexamethasone group and none in the placebo/dexamethasone group.

Stroke (CVA) was reported as a serious (2.3%) or severe (2.0%) adverse drug reaction in the REVLIMID/dexamethasone group compared to 0.9% and 0.9% respectively in the placebo/dexamethasone group. Discontinuation due to stroke (CVA) was 1.4% in REVLIMID/ dexamethasone group and 0.3% in the placebo/dexamethasone group.

Other Adverse Reactions

In these clinical studies of REVLIMID in patients with multiple myeloma, the following adverse drug reactions (ADRs) not described above that occurred at ≥1% rate and of at least twice of the placebo percentage rate were reported:

Blood and lymphatic system disorders: pancytopenia, autoimmune hemolytic anemia

Cardiac disorders: bradycardia, myocardial infarction, angina pectoris

Endocrine disorders: hirsutism

Eye disorders: blindness, ocular hypertension

Gastrointestinal disorders: gastrointestinal hemorrhage, glossodynia

General disorders and administration site conditions: malaise

Investigations: liver function tests abnormal, alanine aminotransferase increased

Nervous system disorders: cerebral ischemia

Psychiatric disorders: mood swings, hallucination, loss of libido

Reproductive system and breast disorders: erectile dysfunction

Respiratory, thoracic and mediastinal disorders: cough, hoarseness

Skin and subcutaneous tissue disorders: exanthem, skin hyperpigmentation

6.2 Clinical Trials Experience in Myelodysplastic Syndromes

A total of 148 patients received at least 1 dose of 10 mg REVLIMID in the del 5q MDS clinical study. At least one adverse event was reported in all of the 148 patients who were treated with the 10 mg starting dose of REVLIMID. The most frequently reported adverse events were related to blood and lymphatic system disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders, and general disorders and administrative site conditions.

Thrombocytopenia (61.5%; 91/148) and neutropenia (58.8%; 87/148) were the most frequently reported adverse events. The next most common adverse events observed were diarrhea (48.6%; 72/148), pruritus (41.9%; 62/148), rash (35.8%; 53/148) and fatigue (31.1%; 46/148). Table 5 summarizes the adverse events that were reported in ≥ 5% of the REVLIMID treated patients in the del 5q MDS clinical study. Table 6 summarizes the most frequently observed Grade 3 and Grade 4 adverse reactions regardless of relationship to treatment with REVLIMID. In the single-arm studies conducted, it is often not possible to distinguish adverse events that are drug-related and those that reflect the patient's underlying disease.

Table 5: Summary of Adverse Events Reported in ≥5% of the REVLIMID Treated Patients in del 5q MDS Clinical Study

System organ class/Preferred term [a]	10 mg Overall (N=148)	
Patients with at least one adverse event	148	(100.0)
Blood and Lymphatic System Disorders		
Thrombocytopenia	91	(61.5)
Neutropenia	87	(58.8)
Anemia	17	(11.5)
Leukopenia	12	(8.1)
Febrile Neutropenia	8	(5.4)
Skin and Subcutaneous Tissue Disorders		
Pruritus	62	(41.9)
Rash	53	(35.8)
Dry Skin	21	(14.2)
Contusion	12	(8.1)
Night Sweats	12	(8.1)
Sweating Increased	10	(6.8)
Ecchymosis	8	(5.4)
Erythema	8	(5.4)
Gastrointestinal Disorders		
Diarrhea	72	(48.6)
Constipation	35	(23.6)
Nausea	35	(23.6)
Abdominal Pain	18	(12.2)
Vomiting	15	(10.1)
Abdominal Pain Upper	12	(8.1)
Dry Mouth	10	(6.8)
Loose Stools	9	(6.1)
Respiratory, Thoracic and Mediastinal Disorders		
Nasopharyngitis	34	(23.0)
Cough	29	(19.6)
Dyspnea	25	(16.9)
Pharyngitis	23	(15.5)
Epistaxis	22	(14.9)
Dyspnea Exertional	10	(6.8)
Rhinitis	10	(6.8)
Bronchitis	9	(6.1)
General Disorders and Administration Site Conditions		
Fatigue	46	(31.1)
Pyrexia	31	(20.9)
Edema Peripheral	30	(20.3)
Asthenia	22	(14.9)
Edema	15	(10.1)
Pain	10	(6.8)
Rigors	9	(6.1)
Chest Pain	8	(5.4)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	32	(21.6)
Back Pain	31	(20.9)
Muscle Cramp	27	(18.2)

Pain in Limb	16	(10.8)
Myalgia	13	(8.8)
Peripheral Swelling	12	(8.1)
Nervous System Disorders		
Dizziness	29	(19.6)
Headache	29	(19.6)
Hypoesthesia	10	(6.8)
Dysgeusia	9	(6.1)
Peripheral Neuropathy	8	(5.4)
Infections and Infestations		
Upper Respiratory Tract Infection	22	(14.9)
Pneumonia	17	(11.5)
Urinary Tract Infection	16	(10.8)
Sinusitis	12	(8.1)
Cellulitis	8	(5.4)
Metabolism and Nutrition Disorders		
Hypokalemia	16	(10.8)
Anorexia	15	(10.1)
Hypomagnesemia	9	(6.1)
Investigations		
Alanine Aminotransferase Increased	12	(8.1)
Psychiatric Disorders		
Insomnia	15	(10.1)
Depression	8	(5.4)
Renal and Urinary Disorders		
Dysuria	10	(6.8)
Vascular Disorders		
Hypertension	9	(6.1)
Endocrine Disorders		
Acquired Hypothyroidism	10	(6.8)
Cardiac Disorders		
Palpitations	8	(5.4)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Table 6: Most Frequently Observed Grade 3 and 4 Adverse Events [1] Regardless of Relationship to Study Drug Treatment

Preferred term [2]	**10 mg (N=148)**	
Patients with at least one Grade 3/4 AE	131	(88.5)
Neutropenia	79	(53.4)
Thrombocytopenia	74	(50.0)
Pneumonia	11	(7.4)
Rash	10	(6.8)
Anemia	9	(6.1)
Leukopenia	8	(5.4)
Fatigue	7	(4.7)
Dyspnea	7	(4.7)
Back Pain	7	(4.7)
Febrile Neutropenia	6	(4.1)
Nausea	6	(4.1)
Diarrhea	5	(3.4)
Pyrexia	5	(3.4)
Sepsis	4	(2.7)
Dizziness	4	(2.7)
Granulocytopenia	3	(2.0)
Chest Pain	3	(2.0)
Pulmonary Embolism	3	(2.0)
Respiratory Distress	3	(2.0)
Pruritus	3	(2.0)
Pancytopenia	3	(2.0)
Muscle Cramp	3	(2.0)
Respiratory Tract Infection	2	(1.4)
Upper Respiratory Tract Infection	2	(1.4)

Asthenia	2	(1.4)
Multi-organ Failure	2	(1.4)
Epistaxis	2	(1.4)
Hypoxia	2	(1.4)
Pleural Effusion	2	(1.4)
Pneumonitis	2	(1.4)
Pulmonary Hypertension	2	(1.4)
Vomiting	2	(1.4)
Sweating Increased	2	(1.4)
Arthralgia	2	(1.4)
Pain in Limb	2	(1.4)
Headache	2	(1.4)
Syncope	2	(1.4)

[1] Adverse events with frequency ≥1% in the 10 mg Overall group. Grade 3 and 4 are based on National Cancer Institute Common Toxicity Criteria version 2.
[2] Preferred Terms are coded using the MedDRA dictionary. A patient with multiple occurrences of an AE is counted only once in the Preferred Term category.

In other clinical studies of REVLIMID in MDS patients, the following serious adverse events (regardless of relationship to study drug treatment) not described in Table 5 or 6 were reported:

Blood and lymphatic system disorders: warm type hemolytic anemia, splenic infarction, bone marrow depression, coagulopathy, hemolysis, hemolytic anemia, refractory anemia

Cardiac disorders: cardiac failure congestive, atrial fibrillation, angina pectoris, cardiac arrest, cardiac failure, cardio-respiratory arrest, cardiomyopathy, myocardial infarction, myocardial ischemia, atrial fibrillation aggravated, bradycardia, cardiogenic shock, pulmonary edema, supraventricular arrhythmia, tachyarrhythmia, ventricular dysfunction

Ear and labyrinth disorders: vertigo

Endocrine disorders: Basedow's disease

Gastrointestinal disorders: gastrointestinal hemorrhage, colitis ischemic, intestinal perforation, rectal hemorrhage, colonic polyp, diverticulitis, dysphagia, gastritis, gastroenteritis, gastroesophageal reflux disease, obstructive inguinal hernia, irritable bowel syndrome, melena, pancreatitis due to biliary obstruction, pancreatitis, perirectal abscess, small intestinal obstruction, upper gastrointestinal hemorrhage

General disorders and administration site conditions: disease progression, fall, gait abnormal, intermittent pyrexia, nodule, rigors, sudden death

Hepatobiliary disorders: hyperbilirubinemia, cholecystitis, acute cholecystitis, hepatic failure

Immune system disorders: hypersensitivity

Infections and infestations infection bacteremia, central line infection, clostridial infection, ear infection, *Enterobacter* sepsis, fungal infection, herpes viral infection NOS, influenza, kidney infection, *Klebsiella* sepsis, lobar pneumonia, localized infection, oral infection, *Pseudomonas* infection, septic shock, sinusitis acute, sinusitis, *Staphylococcal* infection, urosepsis

Injury, poisoning and procedural complications: femur fracture, transfusion reaction, cervical vertebral fracture, femoral neck fracture, fractured pelvis, hip fracture, overdose, post procedural hemorrhage, rib fracture, road traffic accident, spinal compression fracture

Investigations: blood creatinine increased, hemoglobin decreased, liver function tests abnormal, troponin I increased

Metabolism and nutrition disorders: dehydration, gout, hypernatremia, hypoglycemia

Musculoskeletal and connective tissue disorders: arthritis, arthritis aggravated, gouty arthritis, neck pain, chondrocalcinosis pyrophosphate

Neoplasms benign, malignant and unspecified: acute leukemia, acute myeloid leukemia, bronchoalveolar carcinoma, lung cancer metastatic, lymphoma, prostate cancer metastatic

Nervous system disorders: cerebrovascular accident, aphasia, cerebellar infarction, cerebral infarction, depressed level of consciousness, dysarthria, migraine, spinal cord compression, subarachnoid hemorrhage, transient ischemic attack

Psychiatric disorders: confusional state

Renal and urinary disorders: renal failure, hematuria, renal failure acute, azotemia, calculus ureteric, renal mass

Reproductive system and breast disorders: pelvic pain

Respiratory, thoracic and mediastinal disorders: bronchitis, chronic obstructive airways disease exacerbated, respiratory failure, dyspnea exacerbated, interstitial lung disease, lung infiltration, wheezing

Skin and subcutaneous tissue disorders: acute febrile neutrophilic dermatosis

Vascular system disorders: deep vein thrombosis, hypotension, aortic disorder, ischemia, thrombophlebitis superficial, thrombosis

6.3 Clinical Trials Experience in Mantle Cell Lymphoma

In the MCL trial, a total of 134 patients received at least 1 dose of REVLIMID. Their median age was 67 (range 43-83) years, 128/134 (96%) were Caucasian, 108/134 (81%) were males and 82/134 (61%) had duration of MCL for at least 3 years.

Table 7 summarizes the most frequently observed adverse reactions regardless of relationship to treatment with REVLIMID. Across the 134 patients treated in this study, median duration of treatment was 95 days (1-1002 days). Seventy-eight patients (58%) received 3 or more cycles of therapy, 53 patients (40%) received 6 or more cycles, and 26 patients (19%) received 12 or more cycles. Seventy-six patients (57%) underwent at least one dose interruption due to adverse events, and 51 patients (38%) underwent at least one dose reduction due to adverse events. Twenty-six patients (19%) discontinued treatment due to adverse events.

Table 7: Incidence of Adverse Reactions (≥10%) or Grade 3 / 4 AE (in at least 2 patients) in Mantle Cell Lymphoma

System Organ Class/Preferred Term	All AEs[1] (N=134) n (%)	Grade 3/4 AEs[2] (N=134) n (%)
General disorders and administration site conditions		
Fatigue	45 (34)	9 (7)
Pyrexia[$]	31 (23)	3 (2)
Edema peripheral	21 (16)	0
Asthenia[$]	19 (14)	4 (3)
General physical health deterioration	3 (2)	2 (1)
Gastrointestinal disorders		
Diarrhea[$]	42 (31)	8 (6)
Nausea[$]	40 (30)	1 (<1)
Constipation	21 (16)	1 (<1)
Vomiting[$]	16 (12)	1 (<1)
Abdominal pain[$]	13 (10)	5 (4)
Musculoskeletal and connective tissue disorders		
Back pain	18 (13)	2 (1)
Muscle spasms	17 (13)	1 (<1)
Arthralgia	11 (8)	2 (1)
Muscular weakness[$]	8 (6)	2 (1)
Respiratory, thoracic and mediastinal disorders		
Cough	38 (28)	1 (<1)
Dyspnea[$]	24 (18)	8 (6)
Pleural Effusion	10 (7)	2 (1)
Hypoxia	3 (2)	2 (1)
Pulmonary embolism	3 (2)	2 (1)
Respiratory distress[$]	2 (1)	2 (1)

System Organ Class/Preferred Term	All AEs[1] (N=134) n (%)	Grade 3/4 AEs[2] (N=134) n (%)
Oropharyngeal pain	13 (10)	0
Infections and infestations		
Pneumonia[@ $]	19 (14)	12 (9)
Upper respiratory tract infection	17 (13)	0
Cellulitis[$]	3 (2)	2 (1)
Bacteremia[$]	2 (1)	2 (1)
Staphylococcal sepsis[$]	2 (1)	2 (1)
Urinary tract infection[$]	5 (4)	2 (1)
Skin and subcutaneous tissue disorders		
Rash [+]	30 (22)	2 (1)
Pruritus	23 (17)	1 (<1)
Blood and lymphatic system disorders		
Neutropenia	65 (49)	58 (43)
Thrombocytopenia[% $]	48 (36)	37 (28)
Anemia[$]	41 (31)	15 (11)
Leukopenia[$]	20 (15)	9 (7)
Lymphopenia	10 (7)	5 (4)
Febrile neutropenia[$]	8 (6)	8 (6)
Metabolism and nutrition disorders		
Decreased appetite	19 (14)	1 (<1)
Hypokalemia	17 (13)	3 (2)
Dehydration[$]	10 (7)	4 (3)
Hypocalcemia	4 (3)	2 (1)
Hyponatremia	3 (2)	3 (2)
Renal and urinary disorders		
Renal failure[$]	5 (4)	2 (1)
Vascular disorders		
Hypotension[@ $]	9 (7)	4 (3)
Deep vein thrombosis[$]	5 (4)	5 (4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Tumor flare	13 (10)	0
Squamous cell carcinoma of skin[$]	4 (3)	4 (3)
Investigations		
Weight decreased	17 (13)	0

[1]-MCL trial AEs – All treatment emergent AEs with ≥10% of subjects
[2]-MCL trial Grade 3/4 AEs – All treatment-emergent Grade 3/4 AEs in 2 or more subjects
[$]-MCL trial Serious AEs – All treatment-emergent SAEs in 2 or more subjects
[@] - AEs where at least one resulted in a fatal outcome
[%] - AEs where at least one was considered to be Life Threatening (if the outcome of the event was death, it is included with death cases)
[#] - All PTs under SOC of Infections except for rare infections of Public Health interest will be considered listed
[+] - All PTs under HLT of Rash will be considered listed

The following adverse events which have occurred in other indications and not described above have been reported (5-10%) in patients treated with REVLIMID monotherapy for mantle cell lymphoma.

General disorders and administration site conditions: Chills
Musculoskeletal and connective tissue disorders: Pain in extremity
Nervous system disorders: Dysguesia, headache, neuropathy peripheral
Infections and infestations: Respiratory tract infection, sinusitis, nasopharyngitis
Skin and subcutaneous tissue disorders: Dry skin, night sweats

The following serious adverse events not described above and reported in 2 or more patients treated with REVLIMID monotherapy for mantle cell lymphoma.

Respiratory, Thoracic and Mediastinal Disorders: Chronic obstructive pulmonary disease
Infections and Infestations: Clostridium difficile colitis, sepsis
Neoplasms benign, malignant and unspecified (incl cysts and polyps): Basal cell carcinoma
Cardiac Disorder: Supraventricular tachycardia

6.4 Postmarketing Experience

The following adverse drug reactions have been identified from the worldwide post-marketing experience with REVLIMID: Allergic conditions (angioedema, SJS, TEN), tumor lysis syndrome (TLS) and tumor flare reaction (TFR), pneumonitis, hepatic failure, including fatality, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis and transient abnormal liver laboratory tests. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure [*see Warnings and Precautions Section (5.5 to 5.8)*].

Cases of hypothyroidism and hyperthyroidism have also been reported. Optimal control of thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

7 DRUG INTERACTIONS

Results from human in vitro studies show that REVLIMID is neither metabolized by nor inhibits or induces the cytochrome P450 pathway suggesting that lenalidomide is not likely to cause or be subject to P450-based metabolic drug interactions.

In vitro studies demonstrated that REVLIMID is not a substrate of human breast cancer resistance protein (BCRP), multidrug resistance protein (MRP) transporters MRP1, MRP2, or MRP3, organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptide 1B1 (OATP1B1 or OATP2), organic cation transporters (OCT) OCT1 and OCT2, multidrug and toxin extrusion protein (MATE) MATE1, and organic cation transporters novel (OCTN) OCTN1 and OCTN2.

In vitro, lenalidomide is a substrate, but is not an inhibitor of P-glycoprotein (P-gp).

7.1 Digoxin

When digoxin was co-administered with multiple doses of REVLIMID (10 mg/day) the digoxin C_{max} and $AUC_{0-\infty}$ were increased by 14%. Periodic monitoring of digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, is recommended during administration of REVLIMID.

7.2 Warfarin

Co-administration of multiple dose REVLIMID (10 mg) with single dose warfarin (25 mg) had no effect on the pharmacokinetics of total lenalidomide or R- and S-warfarin. Expected changes in laboratory assessments of PT and INR were observed after warfarin administration, but these changes were not affected by concomitant REVLIMID administration. It is not known whether there is an interaction between dexamethasone and warfarin. Close monitoring of PT and INR is recommended in multiple myeloma patients taking concomitant warfarin.

7.3 Concomitant Therapies That May Increase the Risk of Thrombosis

Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution after making a benefit-risk assessment in patients receiving REVLIMID [*see Warnings and Precautions (5.4)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [*see Boxed Warnings and Contraindications (4.1)*]

Risk Summary

REVLIMID can cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy. REVLIMID is a thalidomide analogue.

Thalidomide is a human teratogen, inducing a high frequency of severe and life-threatening birth defects such as amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia, micropinna, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented and mortality at or shortly after birth has been reported in about 40% of infants.

Lenalidomide caused thalidomide-type limb defects in monkey offspring. 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 hazard to a fetus.

If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure to REVLIMID must be reported to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.

Animal data

In an embryo-fetal developmental toxicity study in monkeys, teratogenicity, including thalidomide-like limb defects, occurred in offspring when pregnant monkeys received oral lenalidomide during organogenesis. Exposure (AUC) in monkeys at the lowest dose was 0.17 times the human exposure at the maximum recommended human dose (MRHD) of 25 mg. Similar studies in pregnant rabbits and rats at 20 times and 200 times the MRHD respectively, produced embryo lethality in rabbits and no adverse reproductive effects in rats.

In a pre- and post-natal development study in rats, animals received lenalidomide from organogenesis through lactation. The study revealed a few adverse effects on the offspring of female rats treated with lenalidomide at doses up to 500 mg/kg (approximately 200 times the human dose of 25 mg based on body surface area). The male offspring exhibited slightly delayed sexual maturation and the female offspring had slightly lower body weight gains during gestation when bred to male offspring. As with thalidomide, the rat model may not adequately address the full spectrum of potential human embryo-fetal developmental effects for lenalidomide.

8.3 Nursing mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from lenalidomide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric use

Safety and effectiveness in pediatric patients below the age of 18 have not been established.

8.5 Geriatric use

REVLIMID has been used in multiple myeloma (MM) clinical trials in patients up to 86 years of age.

Of the 703 MM patients who received study treatment in Studies 1 and 2, 45% were age 65 or over while 12% of patients were age 75 and over. The percentage of patients age 65 or over was not significantly different between the REVLIMID/dexamethasone and placebo/dexamethasone groups. Of the 353 patients who received REVLIMID/dexamethasone, 46% were age 65 and over. In both studies, patients > 65 years of age were more likely than patients ≤ 65 years of age to experience DVT, pulmonary embolism, atrial fibrillation, and renal failure following use of REVLIMID. No differences in efficacy were observed between patients over 65 years of age and younger patients.

REVLIMID has been used in del 5q MDS clinical trials in patients up to 95 years of age.

Of the 148 patients with del 5q MDS enrolled in the major study, 38% were age 65 and over, while 33% were age 75 and over. Although the overall frequency of adverse events (100%) was the same in patients over 65 years of age as in younger patients, the frequency of serious adverse events was higher in patients over 65 years of age than in younger patients (54% vs. 33%). A greater proportion of patients over 65 years of age discontinued from the clinical studies because of adverse events than the proportion of younger patients (27% vs.16%). No differences in efficacy were observed between patients over 65 years of age and younger patients.

REVLIMID has been used in a mantle cell lymphoma (MCL) clinical trial in patients up to 83 years of age. Of the 134 patients with MCL enrolled in the MCL trial, 63% were age 65 and over, while 22% of patients were age 75 and over. The overall frequency of adverse events was similar in patients over 65 years of age and in younger patients (98% vs. 100%). The overall incidence of grade 3 and 4 adverse events was also similar in these 2 patient groups (79% vs. 78%, respectively). The frequency of serious adverse events was higher in patients over 65 years of age than in younger patients (55% vs. 41%). No differences in efficacy were observed between patients over 65 years of age and younger patients.

Since elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Monitor renal function.

8.6 Females of Reproductive Potential and Males

REVLIMID can cause fetal harm when administered during pregnancy [*see Use in Specific Populations (8.1)*]. Females of reproductive potential must avoid pregnancy 4 weeks before therapy, while taking REVLIMID, during dose interruptions and for at least 4 weeks after completing therapy.

Females

Females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control simultaneously (one highly effective form of contraception – tubal ligation, IUD, hormonal (birth control pills, injections, hormonal patches, vaginal rings or implants) or partner's vasectomy and one additional effective contraceptive method – male latex or synthetic condom, diaphragm or cervical cap. Contraception must begin 4 weeks prior to initiating treatment with REVLIMID, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of REVLIMID therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. Females of reproductive potential should be referred to a qualified provider of contraceptive methods, if needed.

Females of reproductive potential must have 2 negative pregnancy tests before initiating REVLIMID. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing REVLIMID. Once treatment has started and during dose interruptions, pregnancy testing for females of reproductive potential should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. REVLIMID treatment must be discontinued during this evaluation.

Males
Lenalidomide is present in the semen of males who take REVLIMID. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID, during dose interruptions and for up to 28 days after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm

8.7 Renal Impairment

Since lenalidomide 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 (CLcr 30-60 mL/min) or severe renal impairment (CLcr < 30 mL/min) and in patients on dialysis [*see Dosage and Administration (2.4)*].

8.8 Hepatic Impairment

No dedicated study has been conducted in patients with hepatic impairment. The elimination of unchanged lenalidomide is predominantly by the renal route.

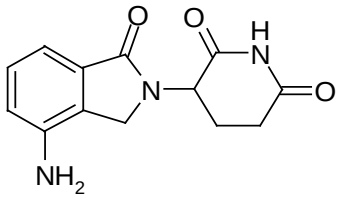
10 OVERDOSAGE

There is no specific experience in the management of lenalidomide overdose in patients; although in dose-ranging studies, some patients were exposed to up to 150 mg and in single-dose studies, some patients were exposed to up to 400 mg.

In studies, the dose-limiting toxicity was essentially hematological. In the event of overdose, supportive care is advised.

11 DESCRIPTION

REVLIMID, a thalidomide analogue, is an immunomodulatory agent with antiangiogenic and antineoplastic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:



3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

REVLIMID is available in 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg and 25 mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The 5 mg and 25 mg capsule shell contains gelatin, titanium dioxide and black ink. The 2.5 mg and 10 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink. The 15 mg capsule shell contains gelatin, FD&C blue #2, titanium dioxide and black ink. The 20 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action

Lenalidomide is an analogue of thalidomide with immunomodulatory, antiangiogenic, and antineoplastic properties. Lenalidomide inhibits proliferation and induces apoptosis of certain hematopoietic tumor cells including multiple myeloma, mantle cell lymphoma, and del (5q) myelodysplastic syndromes *in vitro*. Lenalidomide causes a delay in tumor growth in some *in vivo* nonclinical hematopoietic tumor models including multiple myeloma. Immunomodulatory properties of lenalidomide include activation of T cells and natural killer (NK) cells, increased numbers of NKT cells, and inhibition of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. In multiple myeloma cells, the combination of lenalidomide and dexamethasone synergizes the inhibition of cell proliferation and the induction of apoptosis.

12.2 Pharmacodynamics

The effect of lenalidomide on the QTc interval was evaluated in 60 healthy male subjects in a randomized, thorough QT study with placebo and positive controls. At a dose two times the maximum recommended dose, lenalidomide does not prolong the QTc interval to any clinically relevant extent. The largest upper bound of the 2-sided 90% CI for the mean differences between lenalidomide and placebo was below 10 ms.

12.3 Pharmacokinetics

Absorption

Lenalidomide is rapidly absorbed following oral administration. Following single and multiple doses of REVLIMID in patients with MM or MDS the maximum plasma concentrations occurred between 0.5 and 6 hours post-dose. The single and multiple dose pharmacokinetic disposition of lenalidomide is linear with AUC and C_{max} values increasing proportionally with dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Systemic exposure (AUC) of lenalidomide in MM and MDS patients with normal or mild renal function (CLcr ≥ 60 mL/min) is approximately 60% higher as compared to young healthy male subjects.

Administration of a single 25 mg dose of REVLIMID with a high-fat meal in healthy subjects reduces the extent of absorption, with an approximate 20% decrease in AUC and 50% decrease in C_{max}. In the trials where the efficacy and safety were established for REVLIMID, the drug was administered without regard to food intake. REVLIMID can be administered with or without food.

Population pharmacokinetic analyses show that the oral absorption rate of lenalidomide in patients with MCL is similar to that observed in patients with MM or MDS.

Distribution

In vitro (^{14}C)-lenalidomide binding to plasma proteins is approximately 30%.

Metabolism

Lenalidomide -undergoes limited metabolism. Unchanged lenalidomide is the predominant circulating component in humans. Two identified metabolites are hydroxy-lenalidomide and N-acetyl-lenalidomide; each constitutes less than 5% of parent levels in circulation.

Elimination

Elimination is primarily renal. Following a single oral administration of [^{14}C]-lenalidomide (25 mg) to healthy subjects, approximately 90% and 4% of the radioactive dose is eliminated within ten days in urine and feces, respectively. Approximately 82% of the radioactive dose is excreted as lenalidomide in the urine within 24 hours. Hydroxy-lenalidomide and N-acetyl-lenalidomide represent 4.59% and 1.83% of the excreted dose, respectively. The renal clearance of lenalidomide exceeds the glomerular filtration rate.

The mean half-life of lenalidomide is 3 hours in healthy subjects and 3 to 5 hours in patients with MM, MDS or MCL.

Effect of Dexamethasone

Co-administration of single or multiple doses of dexamethasone (40 mg) has no clinically relevant effect on the multiple dose pharmacokinetics of REVLIMID (25 mg).

Specific Populations

Patients with Renal Impairment: The pharmacokinetics of lenalidomide were studied in patients with renal impairment due to nonmalignant conditions. In this study, 5 patients with mild renal impairment (creatinine clearance 57-74 mL/min), 6 patients with moderate renal impairment (creatinine clearance 33-46 mL/min), 6 patients with severe renal impairment (creatinine clearance 17-29 mL/min), and 6 patients with end stage renal disease requiring dialysis were administered a single oral 25-mg dose of REVLIMID. As a control group comparator, 7 healthy subjects of similar age with normal renal function (creatinine clearance 83-145 mL/min) were also administered a single oral 25-mg dose of REVLIMID. As creatinine clearance decreased from mild to severe impairment, half-life increased and drug clearance decreased linearly. Patients with moderate and severe renal impairment had a 3-fold increase in half-life and a 66% to 75% decrease in drug clearance compared to healthy subjects. Patients on hemodialysis (n=6) given a single, 25-mg dose of lenalidomide has an approximate 4.5-fold increase in half-life and an 80% decrease in drug clearance compared to healthy subjects. Approximately 40% of the administered dose was removed from the body during a single dialysis session.

In MM patients, those patients with mild renal impairment had an AUC 56% greater than those with normal renal function.

Adjustment of the starting dose of REVLIMID is recommended in patients with moderate or severe (CLcr < 60 mL/min) renal impairment and in patients on dialysis [*see Dosage and Administration (2.4)*].

Elderly Patients: No dedicated clinical studies have been conducted to evaluate pharmacokinetics of lenalidomide in the elderly. Population pharmacokinetic analyses included patients with ages ranging from 39 to 85 years old and show that age does not influence the disposition of lenalidomide.

Patients with Hepatic Disease: Population pharmacokinetic analyses included patients with mild hepatic impairment (N = 16, total bilirubin >1 to ≤ 1.5 x ULN or AST > ULN) and show that mild hepatic impairment does not influence the disposition of lenalidomide. There are no data available for patients with moderate to severe hepatic impairment.

Pediatric: No pharmacokinetic data are available in patients below the age of 18 years.

Other Intrinsic Factors: Population pharmacokinetic analyses show that body weight (33-135 kg), gender, race, and type of hematological malignancies (MM, MDS or MCL) do not have a clinically relevant effect on lenalidomide clearance in adult patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenicity studies with lenalidomide have not been conducted.

Lenalidomide was not mutagenic in the bacterial reverse mutation assay (Ames test) and did not induce chromosome aberrations in cultured human peripheral blood lymphocytes, or mutations at the thymidine kinase (tk) locus of mouse lymphoma L5178Y cells. Lenalidomide did not increase morphological transformation in Syrian Hamster Embryo assay or induce micronuclei in the polychromatic erythrocytes of the bone marrow of male rats.

A fertility and early embryonic development study in rats, with administration of lenalidomide up to 500 mg/kg (approximately 200 times the human dose of 25 mg, based on body surface area) produced no parental toxicity and no adverse effects on fertility.

14 CLINICAL STUDIES

14.1 Multiple Myeloma

Two randomized studies (Studies 1 and 2) were conducted to evaluate the efficacy and safety of REVLIMID. These multicenter, multinational, double-blind, placebo-controlled studies compared REVLIMID plus oral pulse high-dose dexamethasone therapy to dexamethasone therapy alone in patients with multiple myeloma who had received at least one prior treatment. These studies enrolled patients with absolute neutrophil counts (ANC) $\geq 1000/mm^3$, platelet counts $\geq 75{,}000/mm^3$, serum creatinine ≤ 2.5 mg/dL, serum SGOT/AST or SGPT/ALT ≤ 3 x upper limit of normal (ULN), and serum direct bilirubin ≤ 2 mg/dL.

In both studies, patients in the REVLIMID/dexamethasone group took 25 mg of REVLIMID orally once daily on Days 1 to 21 and a matching placebo capsule once daily on Days 22 to 28 of each 28-day cycle. Patients in the placebo/dexamethasone group took 1 placebo capsule on Days 1 to 28 of each 28-day cycle. Patients in both treatment groups took 40 mg of dexamethasone orally once daily on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy.

The dose of dexamethasone was reduced to 40 mg orally once daily on Days 1 to 4 of each 28-day cycle after the first 4 cycles of therapy. In both studies, treatment was to continue until disease progression.

In both studies, dose adjustments were allowed based on clinical and laboratory findings. Sequential dose reductions to 15 mg daily, 10 mg daily and 5 mg daily were allowed for toxicity [*see Dosage and Administration (2.1)*].

Table 8 summarizes the baseline patient and disease characteristics in the two studies. In both studies, baseline demographic and disease-related characteristics were comparable between the REVLIMID/dexamethasone and placebo/dexamethasone groups.

Table 8: Baseline Demographic and Disease-Related Characteristics – Studies 1 and 2

	Study 1		Study 2	
	REVLIMID/Dex N=177	**Placebo/Dex N=176**	**REVLIMID/Dex N=176**	**Placebo/Dex N=175**
Patient Characteristics				
Age (years) Median Min, Max	 64 36, 86	 62 37, 85	 63 33, 84	 64 40, 82
Sex Male Female	 106 (60%) 71 (40%)	 104 (59%) 72 (41%)	 104 (59%) 72 (41%)	 103 (59%) 72 (41%)
Race/Ethnicity White Other	 141(80%) 36 (20%)	 148 (84%) 28 (16%)	 172 (98%) 4 (2%)	 175(100%) 0 (0%)
ECOG Performance Status 0-1	 157 (89%)	 168 (95%)	 150 (85%)	 144 (82%)
Disease Characteristics				
Multiple Myeloma Stage (Durie-Salmon) I II III	 3% 32% 64%	 3% 31% 66%	 6% 28% 65%	 5% 33% 63%

B2-microglobulin (mg/L) ≤ 2.5 mg/L > 2.5 mg/L	52 (29%) 125 (71%)	51 (29%) 125 (71%)	51 (29%) 125 (71%)	48 (27%) 127 (73%)
Number of Prior Therapies				
1 ≥ 2	38% 62%	38% 62%	32% 68%	33% 67%
Types of Prior Therapies				
Stem Cell Transplantation	62%	61%	55%	54%
Thalidomide	42%	46%	30%	38%
Dexamethasone	81%	71%	66%	69%
Bortezomib	11%	11%	5%	4%
Melphalan	33%	31%	56%	52%
Doxorubicin	55%	51%	56%	57%

The primary efficacy endpoint in both studies was time to progression (TTP). TTP was defined as the time from randomization to the first occurrence of progressive disease.

Preplanned interim analyses of both studies showed that the combination of REVLIMID/dexamethasone was significantly superior to dexamethasone alone for TTP. The studies were unblinded to allow patients in the placebo/dexamethasone group to receive treatment with the REVLIMID/dexamethasone combination. For both studies, the extended follow-up survival data with crossovers were analyzed. In study 1, the median survival time was 39.4 months (95%CI: 32.9, 47.4) in REVLIMID/dexamethasone group and 31.6 months (95%CI: 24.1, 40.9) in placebo/dexamethasone group, with a hazard ratio of 0.79 (95% CI: 0.61-1.03). In study 2, the median survival time was 37.5 months (95%CI: 29.9, 46.6) in REVLIMID/dexamethasone group and 30.8 months (95%CI: 23.5, 40.3) in placebo/dexamethasone group, with a hazard ratio of 0.86 (95% CI: 0.65-1.14).

Table 9: TTP Results in Study 1 and Study 2

	Study 1		**Study 2**	
	REVLIMID/Dex N=177	**Placebo/Dex N=176**	**REVLIMID/Dex N=176**	**Placebo/Dex N=175**
TTP				
Events n (%)	73 (41)	120 (68)	68 (39)	130 (74)
Median TTP in months [95% CI]	13.9 [9.5, 18.5]	4.7 [3.7, 4.9]	12.1 [9.5, NE]	4.7 [3.8, 4.8]
Hazard Ratio [95% CI]	0.285 [0.210, 0.386]		0.324 [0.240, 0.438]	
Log-rank Test p-value [3]	<0.001		<0.001	
Response				
Complete Response (CR) n (%)	23 (13)	1 (1)	27 (15)	7 (4)
Partial Response (RR/PR) n (%)	84 (48)	33 (19)	77 (44)	34 (19)
Overall Response n (%)	107 (61)	34 (19)	104 (59)	41 (23)
p-value	<0.001		<0.001	
Odds Ratio [95% CI]	6.38 [3.95, 10.32]		4.72 [2.98, 7.49]	

Figure 1: Kaplan-Meier Estimate of Time to Progression — Study 1

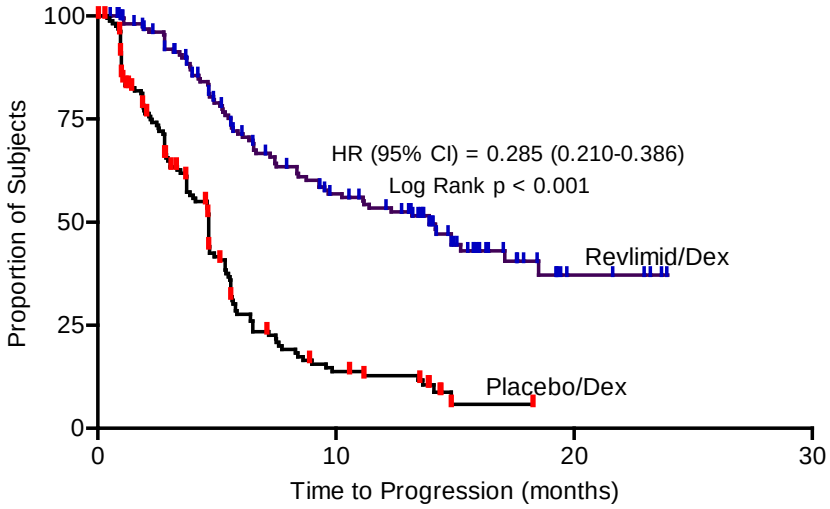
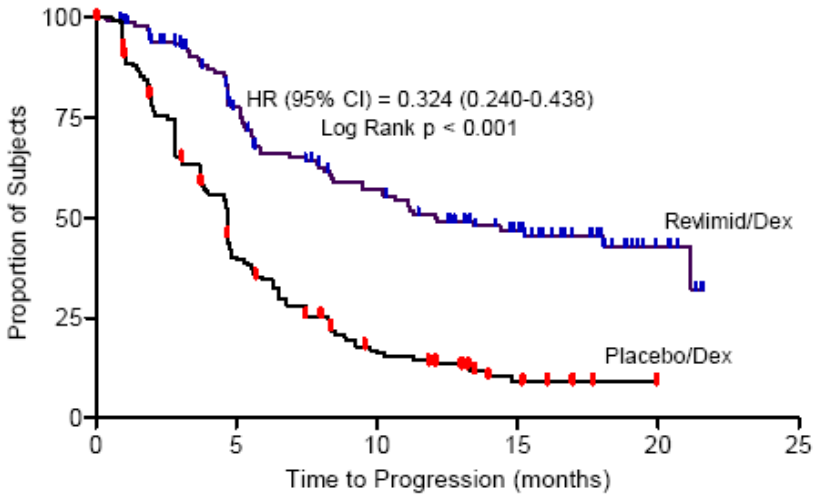


Figure 2: Kaplan-Meier Estimate of Time to Progression — Study 2



14.2 Myelodysplastic Syndromes (MDS) with a Deletion 5q Cytogenetic Abnormality

The efficacy and safety of REVLIMID were evaluated in patients with transfusion-dependent anemia in low- or intermediate-1- risk MDS with a 5q (q31-33) cytogenetic abnormality in isolation or with additional cytogenetic abnormalities, at a dose of 10 mg once daily or 10 mg once daily for 21 days every 28 days in an open-label, single-arm, multi-center study. The major study was not designed nor powered to prospectively compare the efficacy of the 2 dosing regimens. Sequential dose reductions to 5 mg daily and 5 mg every other day, as well as dose delays, were allowed for toxicity [*Dosage and Administration (2.2)*].

This major study enrolled 148 patients who had RBC transfusion dependent anemia. RBC transfusion dependence was defined as having received ≥ 2 units of RBCs within 8 weeks prior to study treatment. The study enrolled patients with absolute neutrophil counts (ANC) ≥ 500/mm^3, platelet counts ≥ 50,000/mm^3, serum creatinine ≤ 2.5 mg/dL, serum SGOT/AST or SGPT/ALT ≤ 3 x upper limit of normal (ULN), and serum direct bilirubin ≤ 2 mg/dL. Granulocyte colony-stimulating factor was permitted for patients who developed neutropenia or fever in association with neutropenia. Baseline patient and disease-related characteristics are summarized in Table 10.

Table 10: Baseline Demographic and Disease-Related Characteristics in the MDS Study

	Overall (N=148)	
Age (years)		
Median	71.0	
Min, Max	37.0, 95.0	
Gender	**n**	**(%)**
Male	51	(34.5)
Female	97	(65.5)
Race	**n**	**(%)**
White	143	(96.6)
Other	5	(3.4)
Duration of MDS (years)		
Median	2.5	
Min, Max	0.1, 20.7	
Del 5 (q31-33) Cytogenetic Abnormality	**n**	**(%)**
Yes	148	(100.0)
Other cytogenetic abnormalities	37	(25.2)
IPSS Score [a]	**n**	**(%)**
Low (0)	55	(37.2)
Intermediate-1 (0.5-1.0)	65	(43.9)
Intermediate-2 (1.5-2.0)	6	(4.1)
High (≥2.5)	2	(1.4)
Missing	20	(13.5)
FAB Classification [b] from central review	**n**	**(%)**
RA	77	(52.0)
RARS	16	(10.8)
RAEB	30	(20.3)
CMML	3	(2.0)

[a] IPSS Risk Category: Low (combined score = 0), Intermediate-1 (combined score = 0.5 to 1.0), Intermediate-2 (combined score = 1.5 to 2.0), High (combined score ≥ 2.5); Combined score = (Marrow blast score + Karyotype score + Cytopenia score)
[b] French-American-British (FAB) classification of MDS.

The frequency of RBC transfusion independence was assessed using criteria modified from the International Working Group (IWG) response criteria for MDS. RBC transfusion independence was defined as the absence of any RBC transfusion during any consecutive "rolling" 56 days (8 weeks) during the treatment period.

Transfusion independence was seen in 99/148 (67%) patients (95% CI [59, 74]). The median duration from the date when RBC transfusion independence was first declared (i.e., the last day of the 56-day RBC transfusion-free period) to the date when an additional transfusion was received after the 56-day transfusion-free period among the 99 responders was 44 weeks (range of 0 to >67 weeks). Ninety percent of patients who achieved a transfusion benefit did so by completion of three months in the study.

RBC transfusion independence rates were unaffected by age or gender.

The dose of REVLIMID was reduced or interrupted at least once due to an adverse event in 118 (79.7%) of the 148 patients; the median time to the first dose reduction or interruption was 21 days (mean, 35.1 days; range, 2-253 days), and the median duration of the first dose interruption was 22 days (mean, 28.5 days; range, 2-265 days). A second dose reduction or interruption due to adverse events was required in 50 (33.8%) of the 148 patients. The median interval between the first and second dose reduction or interruption was 51 days (mean, 59.7 days; range, 15-205 days) and the median duration of the second dose interruption was 21 days (mean, 26 days; range, 2-148 days).

14.3 Mantle Cell Lymphoma

A multicenter, single-arm, open-label trial of single-agent lenalidomide was conducted to evaluate the safety and efficacy of lenalidomide in patients with mantle cell lymphoma who have relapsed after or were refractory to bortezomib or a bortezomib-containing regimen. Patients with a creatinine clearance ≥60 mL/min were given lenalidomide at a dose of 25 mg once daily for 21 days every 28 days. Patients with a creatinine clearance ≥30 mL/min and <60 mL/min were given lenalidomide at a dose of 10 mg once daily for 21 days every 28 days. Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent.

The trial included patients who were at least 18 years of age with biopsy-proven MCL with measurable disease by CT scan. Patients were required to have received prior treatment with an anthracycline or mitoxantrone, cyclophosphamide, rituximab, and bortezomib, alone or in combination. Patients were required to have documented refractory disease (defined as without any response of PR or better during treatment with bortezomib or a bortezomib-containing regimen), or relapsed disease (defined as progression within one year after treatment with bortezomib or a bortezomib-containing regimen). At enrollment patients were to have an absolute neutrophil counts (ANC) ≥1500/ mm^3, platelet counts ≥ 60,000/mm^3, serum SGOT/AST or SGPT/ALT ≤3x upper limit of normal (ULN) unless there was documented evidence of liver involvement by lymphoma, serum total bilirubin ≤1.5 x ULN except in cases of Gilbert's syndrome or documented liver involvement by lymphoma, and calculated creatinine clearance (Cockcroft-Gault formula) ≥30 mL/min.

The median age was 67 years (43-83), 81% were male and 96% were Caucasian. The table below summarizes the baseline disease-related characteristics and prior anti-lymphoma therapy in the Mantle Cell Lymphoma trial.

Table 11: Baseline Disease-related Characteristics and Prior Anti –Lymphoma Therapy in Mantle Cell Lymphoma Trial

Baseline Disease Characteristics and Prior Anti - Lymphoma Treatment	Total Patients (N=134)
ECOG Performance Status[a] n (%)	
0	43 (32)
1	73 (54)
2	17 (13)
3	1 (<1)
Advanced MCL Stage, n (%)	
III	27 (20)
IV	97 (72)
High or Intermediate MIPI Score[b], n (%)	90 (67)
High Tumor Burden[c], n (%)	77 (57)
Bulky Disease[d], n (%)	44 (33)
Extranodal Disease	101 (75)
Number of Prior Systemic Anti-Lymphoma Therapies, n (%)	
Median (range)	4 (2, 10)
1	0 (0)
2	29 (22)
3	34 (25)
≥ 4	71 (53)
Number of Subjects Who Received Prior Regimen Containing, n (%):	
Anthracycline/mitoxantrone	133 (99)
Cyclophosphamide	133 (99)
Rituximab	134 (100)
Bortezomib	134 (100)
Refractory to Prior Bortezomib	81 (60)
Refractory to Last Prior Therapy	74 (55)
Prior Autologous Bone Marrow or Stem Cell Transplant, n (%)	39 (29)

[a] ECOG = Eastern Cooperative Oncology Group
[b] MIPI = MCL International Prognostic Index
[c] High tumor burden is defined as at least one lesion that is ≥5 cm in diameter or 3 lesions that are ≥3 cm in diameter
[d] Bulky disease is defined as at least one lesion that is ≥7cm in the longest diameter

The efficacy endpoints in the MCL trial were overall response rate (ORR) and duration of response (DOR). Response was determined based on review of radiographic scans by an independent review committee according to a modified version of the International Workshop Lymphoma Response Criteria (Cheson, 1999). The DOR is defined as the time from the initial response (at least PR) to documented disease progression. The efficacy results for the MCL population were based on all evaluable patients who received at least one dose of study drug and are presented in Table 12. The median time to response was 2.2 months (range 1.8 to 13 months).

Table 12: Response Outcomes in the Pivotal Mantle Cell Lymphoma Trial

Response Analyses (N = 133)	**N (%)**	**95% CI**
Overall Response Rate (IWRC) (CR + CRu +PR)	34 (26)	(18.4, 33.9)
Complete Response (CR + CRu)	9 (7)	(3.1, 12.5)
CR	1 (1)	
CRu	8 (6)	
Partial Response (PR)	25 (19)	
Duration of Response (months)	**Median**	**95% CI**
Duration of Overall Response (CR + CRu + PR) (N = 34)	16.6	(7.7, 26.7)

15 REFERENCES

1. OSHA Hazardous Drugs. *OSHA* [Accessed on 29 January 2013, from http://www.osha.gov/SLTC/hazardousdrugs/index.html]

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

White and blue-green opaque hard capsules imprinted “REV” on one half and “2.5 mg” on the other half in black ink:

2.5 mg bottles of 28 (NDC 59572-402-28)

2.5 mg bottles of 100 (NDC 59572-402-00)

White opaque capsules imprinted “REV” on one half and “5 mg” on the other half in black ink:

5 mg bottles of 28 (NDC 59572-405-28)

5 mg bottles of 100 (NDC 59572-405-00)

Blue/green and pale yellow opaque capsules imprinted “REV” on one half and “10 mg” on the other half in black ink:

10 mg bottles of 28 (NDC 59572-410-28)

10 mg bottles of 100 (NDC 59572-410-00)

Powder blue and white opaque capsules imprinted “REV” on one half and “15 mg” on the other half in black ink:

15 mg bottles of 21 (NDC 59572-415-21)

15 mg bottles of 100 (NDC 59572-415-00)

Powder blue and blue-green opaque hard capsules imprinted “REV” on one half and “20 mg” on the other half in black ink.

20 mg bottles of 21 (NDC 59572-420-21)

20 mg bottles of 100 (NDC 59572-420-00)

White opaque capsules imprinted “REV” on one half and “25 mg” on the other half in black ink:

25 mg bottles of 21 (NDC 59572-425-21)

25 mg bottles of 100 (NDC 59572-425-00)

16.2 Storage

Store at 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F) [See USP Controlled Room Temperature].

16.3 Handling and Disposal

Care should be exercised in the handling of REVLIMID. REVLIMID capsules should not be opened or crushed. If powder from REVLIMID contacts the skin, wash the skin immediately and thoroughly with soap and water. If REVLIMID contacts the mucous membranes, flush thoroughly with water.

Procedures for the proper handling and disposal of anticancer drugs should be considered. Several guidelines on the subject have been published.[1]

Dispense no more than a 28-day supply.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient labeling (Medication Guide)

Embryo-Fetal Toxicity

Advise patients that REVLIMID is contraindicated in pregnancy [*see Contraindicatons (4.1)*]. REVLIMID is a thalidomide analog and can cause serious birth defects or death to a developing baby. [*see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)*].

- Advise females of reproductive potential that they must avoid pregnancy while taking REVLIMID and for at least 4 weeks after completing therapy.
- Initiate REVLIMID treatment in females of reproductive potential only following a negative pregnancy test.
- Advise females of reproductive potential of the importance of monthly pregnancy tests and the need to use two different forms of contraception including at least one highly effective form simultaneously during REVLIMID therapy, during dose interruption and for 4 weeks after she has completely finished taking REVLIMID. Highly effective forms of contraception other than tubal ligation include IUD and hormonal (birth control pills, injections, patch or implants) and a partner’s vasectomy. Additional effective contraceptive methods include latex or synthetic condom, diaphragm and cervical cap.
- Instruct patient to immediately stop taking REVLIMID and contact her doctor if she becomes pregnant while taking this drug, if she misses her menstrual period, or experiences unusual menstrual bleeding, if she stops taking birth control, or if she thinks FOR ANY REASON that she may be pregnant.

- Advise patient that if her doctor is not available, she can call 1-888-668-2528 for information on emergency contraception [*see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)*].
- Advise males to always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 28 days after discontinuing REVLIMID, even if they have undergone a successful vasectomy.
- Advise male patients taking REVLIMID that they must not donate sperm [*see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)*].
- All patients must be instructed to not donate blood while taking REVLIMID, during dose interruptions and for 1 month following discontinuation of REVLIMID [*see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)*].

REVLIMID REMS™ program

Because of the risk of embryo-fetal toxicity, REVLIMID is only available through a restricted program called the REVLIMID REMS™ program **(formerly known as the "RevAssist®" program)** [*see Warnings and Precautions (5.2)*].

- Patients must sign a Patient-Physician agreement form and comply with the requirements to receive REVLIMID. In particular, females of reproductive potential must comply with the pregnancy testing, contraception requirements and participate in monthly telephone surveys. Males must comply with the contraception requirements [*see Use in Specific Populations (8.6)*].
- REVLIMID is available only from pharmacies that are certified in REVLIMID REMS™ program. Provide patients with the telephone number and website for information on how to obtain the product.

Hematologic Toxicity

Inform patients that REVLIMID is associated with significant neutropenia and thrombocytopenia [*see Boxed Warnings and Warnings and Precautions (5.3)*].

Venous and Arterial Thromboembolism

Inform patients of the risk of thrombosis including DVT, PE, MI, and stroke and to report immediately any signs and symptoms suggestive of these events for evaluation [*see Boxed Warnings and Warning and Precautions (5.4)*].

Increased Mortality in Patients with CLL

Inform patients that REVLIMID had increased mortality in patients with CLL and serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure [*see Warning and Precautions (5.5)*].

Second Primary Malignancies

Inform patients of the potential risk of developing second primary malignancies during treatment with REVLIMID.

Hepatotoxicity

Inform patients of the risk of hepatotoxicity, including hepatic failure and death, and to report any signs and symptoms associated with this event to their healthcare provider for evaluation.

Allergic Reactions

Inform patients of the potential for allergic reactions including hypersensitivity, angioedema, Stevens Johnsons Syndrome, or toxic epidermal necrolysis if they had such a reaction to THALOMID and report symptoms associated with these events to their healthcare provider for evaluation.

Tumor Lysis Syndrome

Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation.

Tumor Flare Reaction

Inform patients of the potential risk of tumor flare reaction and to report any signs and symptoms associated with this event to their healthcare provider for evaluation.

Dosing Instructions

Inform patients to take REVLIMID once daily at about the same time each day, either with or without food. The capsules should not be opened, broken, or chewed. REVLIMID should be swallowed whole with water.

Instruct patients that if they miss a dose of REVLIMID, they may still take it up to 12 hours after the time they would normally take it. If more than 12 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take REVLIMID at the usual time. Warn patients to not take 2 doses to make up for the one that they missed.

Manufactured for: Celgene Corporation
Summit, NJ 07901

RevPlyPI.0XX/MG.0XX XX/14

MEDICATION GUIDE
REVLIMID® (rev-li-mid)
(lenalidomide)
capsules

What is the most important information I should know about REVLIMID?

- Before you begin taking REVLIMID, you must read and agree to all of the instructions in the REVLIMID REMS™ program (formerly known as the RevAssist® program).

- REVLIMID may cause serious side effects including:

Possible birth defects (deformed babies) or death of an unborn baby. Females who are pregnant or who plan to become pregnant must not take REVLIMID.

REVLIMID is similar to the medicine thalidomide (THALOMID®). We know thalidomide can cause severe life-threatening birth defects. REVLIMID has not been tested in pregnant females. REVLIMID has harmed unborn animals in animal testing.

Females must not get pregnant:
- for 4 weeks before starting REVLIMID
- while taking REVLIMID
- during any breaks (interruptions) in your treatment with REVLIMID
- for 4 weeks after stopping REVLIMID

If you become pregnant while taking REVLIMID, stop taking it right away and call your healthcare provider. If your healthcare provider is not available, you can call 1-888-668-2528 for medical information.
Healthcare providers and patients should report all cases of pregnancy to:
- FDA MedWatch at 1-800-FDA-1088, and
- Celgene Corporation at 1-888-423-5436

REVLIMID can pass into human semen:

- Males, including those who have had a vasectomy, must use a latex or synthetic condom during any sexual contact with a pregnant female or a female who can become pregnant while taking REVLIMID, during any breaks (interruptions) in your treatment with REVLIMID, and for 4 weeks after stopping REVLIMID.
- Do not have unprotected sexual contact with a female who is or could become pregnant. Tell your healthcare provider if you do have unprotected sexual contact with a female who is or could become pregnant.
- Do not donate sperm while taking REVLIMID, during any breaks (interruptions) in your treatment, and for 4 weeks after stopping REVLIMID. If a female becomes pregnant with your sperm, the baby may be exposed to REVLIMID and may be born with birth defects.

Men, if your female partner becomes pregnant, you should call your healthcare provider right away.

- **Low white blood cells (neutropenia) and low platelets (thrombocytopenia).**
  REVLIMID causes low white blood cells and low platelets in most people. You may need a blood transfusion or certain medicines if your blood counts drop too low. If you are being treated for deletion 5q myelodysplastic syndromes (MDS) your blood counts should be checked weekly during the first 8 weeks of treatment with REVLIMID, and at least monthly thereafter. If you are being treated for multiple myeloma, your blood counts should be checked every 2 weeks for the first 12 weeks and then at least monthly thereafter.

- **Blood clots.** Blood clots in the arteries, veins, and lungs happen more often in people who take REVLIMID. This risk is even higher for people with multiple myeloma who take the medicine dexamethasone with REVLIMID. Heart attacks and strokes also happen more often in people who take REVLIMID with dexamethasone. To reduce this increased risk, most people who take REVLIMID will also take a blood thinner medicine.

  Before taking REVLIMID, tell your healthcare provider:
  - o if you have had a blood clot in the past
  - o if you have high blood pressure
  - o if you smoke
  - o if you have been told that you have a high level of fat in your blood (hyperlipidemia)
  - o about all the medicines you take. Certain other medicines can also increase your risk for blood clots.

  Call your healthcare provider or get medical help right away if you get any of the following during treatment with REVLIMID:
  - o **signs or symptoms of a blood clot in the lung, arm, or leg may include**: shortness of breath, chest pain, or arm or leg swelling
  - o **signs or symptoms of a heart attack may include**: chest pain that may spread to the arms, neck, jaw, back, or stomach-area (abdomen), feeling sweaty, shortness of breath, feeling sick or vomiting
  - o **signs or symptoms of stroke may include:** sudden numbness or weakness, especially on one side of the body, severe headache or confusion, or problems with vision, speech, or balance.

What is REVLIMID?

REVLIMID is a prescription medicine used to treat people:

- with multiple myeloma (MM) who have received at least one prior medicine, taken along with the medicine dexamethasone.
- who have a condition called myelodysplastic syndromes (MDS). REVLIMID is for the type of MDS with a chromosome problem where part of chromosome 5 is missing. This type of MDS is known as deletion 5q MDS. People with this type of

MDS may have low red blood cell counts that require treatment with blood transfusions.
- with mantle cell lymphoma (MCL) when the disease comes back or becomes worse after treatment with two prior medicines, one of which included bortezomib. Mantle cell lymphoma is a cancer of a type of white blood cell called lymphocytes that are in the lymph nodes.

REVLIMID should not be used to treat people who have chronic lymphocytic leukemia (CLL) unless they are participants in a controlled clinical trial.

It is not known if REVLIMID is safe and effective in children under 18 years of age.

Who should not take REVLIMID?

- Do not take REVLIMID if you are pregnant, plan to become pregnant, or become pregnant during REVLIMID treatment. See "What is the most important information I should know about REVLIMID?"
- Do not take REVLIMID if you are allergic to lenalidomide or any of the ingredients in REVLIMID. See the end of this Medication Guide for a complete list of ingredients in REVLIMID.

What should I tell my healthcare provider before taking REVLIMID?

See "What is the most important information I should know about REVLIMID?"
Before you take REVLIMID, tell your healthcare provider if you:

- have liver problems
- have kidney problems or receive kidney dialysis treatment
- are lactose intolerant. REVLIMID contains lactose.
- have any other medical condition
- **are breastfeeding.** REVLIMID must not be used by females who are breastfeeding. It is not known if REVLIMID passes into your breast milk and can harm your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. REVLIMID and other medicines may affect each other causing serious side effects.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist.

How should I take REVLIMID?

Take REVLIMID exactly as prescribed and follow all the instructions of the REVLIMID REMS™ program (formerly known as the RevAssist® program).

Before prescribing REVLIMID, your healthcare provider will:

- explain the REVLIMID REMS™ program to you
- have you sign the Patient-Physician Agreement Form

- Swallow REVLIMID capsules whole with water 1 time a day. **Do not break, chew, or open your capsules.**
- Take REVLIMID at about the same time each day.
- Do not open the REVLIMID capsules or handle them any more than needed. If you touch a broken REVLIMID capsule or the medicine in the capsule, wash the area of your body with soap and water.
- If you miss a dose of REVLIMID, and it has been less than 12 hours since your regular time, take it as soon as you remember. If it has been more than 12 hours, just skip your missed dose. Do **not** take 2 doses at the same time.
- If you take too much REVLIMID or overdose, call your healthcare provider right away.

Females who can become pregnant:

- will have pregnancy tests weekly for 4 weeks, then every 4 weeks if your menstrual cycle is regular, or every 2 weeks if your menstrual cycle is irregular.
- If you miss your period or have unusual bleeding, you will need to have a pregnancy test and receive counseling.
- must agree to use 2 different forms of effective birth control at the same time every time, for 4 weeks before, while taking, during any breaks (interruptions) in your treatment, and for 4 weeks after stopping REVLIMID.

Males who take REVLIMID, even those who have had a vasectomy, must agree to use a latex or synthetic condom during sexual contact with a pregnant female or a female who can become pregnant.

What should I avoid while taking REVLIMID?

- See “What is the most important information I should know about REVLIMID?”
- **Females: Do not get pregnant and do not breastfeed while taking REVLIMID.**
- **Males: Do not donate sperm.**
- **Do not share REVLIMID with other people.** It may cause birth defects and other serious problems.
- **Do not donate blood** while you take REVLIMID, during any breaks (interruptions) in your treatment, and for 4 weeks after stopping REVLIMID. If someone who is pregnant gets your donated blood, her baby may be exposed to REVLIMID and may be born with birth defects.

What are the possible side effects of REVLIMID?

REVLIMID may cause serious side effects, including:

- See “What is the most important information I should know about REVLIMID?”
- **Increased risk of death in people who have chronic lymphocytic leukemia (CLL).** People with CLL who take REVLIMID have an increased risk of death compared with people who take the medicine chlorambucil. REVLIMID may cause you to have serious heart problems that can lead to death, including atrial fibrillation, heart attack, or heart failure. You should not take REVLIMID if you have CLL unless you are participating in a controlled clinical trial.

- **Risk of new cancers (malignancies).** People with multiple myeloma who receive melphalan (a type of chemotherapy) and a blood stem cell transplant with the addition of REVLIMID have a higher risk of developing new cancers, including certain blood cancers (acute myelogenous leukemia or AML) and a type of lymphoma called Hodgkin lymphoma. Talk with your healthcare provider about your risk of developing new cancers if you take REVLIMID. Your healthcare provider will check you for new cancers during your treatment with REVLIMID.
- **Severe liver problems, including liver failure and death.** Tell your healthcare provider right away if you develop any of the following symptoms of liver problems:
  - yellowing of your skin or the white part of your eyes (jaundice)
  - dark or brown (tea colored) urine
  - pain on the upper right side of your stomach area (abdomen)
  - bleeding or bruising more easily than normal
  - feeling very tired

  Your healthcare provider will do blood tests to check your liver function during your treatment with REVLIMID.
- **Serious skin reactions.** Serious skin reactions can happen with REVLIMID and may cause death. Call your healthcare provider right away if you have any skin reaction while taking REVLIMID.
- **Tumor lysis syndrome (TLS).** TLS is caused by the fast breakdown of cancer cells. TLS can cause kidney failure and the need for dialysis treatment, abnormal heart rhythm, seizure and sometimes death. Your healthcare provider may do blood tests to check you for TLS.
- **Worsening of your tumor (tumor flare reaction)**. Tell your healthcare provider if you get any of these symptoms of tumor flare reaction while taking REVLIMID: tender swollen lymph nodes, low-grade fever, pain, or rash.

REVLIMID may cause serious side effects, including:

- See “What is the most important information I should know about REVLIMID?”

Common side effects of REVLIMID include:

- diarrhea
- itching
- rash
- tiredness

These are not all the possible side effects of REVLIMID.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store REVLIMID?

- Store REVLIMID at room temperature between 68°F to 77°F (20°C to 25°C).

- Return any unused REVLIMID to Celgene or your healthcare provider.

Keep REVLIMID and all medicines out of the reach of children.

General information about REVLIMID

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Do not** take REVLIMID for conditions for which it was not prescribed. **Do not** give REVLIMID to other people, even if they have the same symptoms you have. It may harm them and may cause birth defects.

If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about REVLIMID that is written for health professionals.

For more information, call 1-888-423-5436 or go to www.celgeneriskmanagement.com.

What are the ingredients in REVLIMID?

Active ingredient: lenalidomide
Inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

The 5 mg and 25 mg capsule shells contain gelatin, titanium dioxide and black ink. The 2.5 and 10 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink. The 15 mg capsule shell contains gelatin, FD&C blue #2, titanium dioxide and black ink. The 20 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured for:
Celgene Corporation
Summit, NJ 07901

Revised 2014

Pat. http://www.celgene.com/products.aspx

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