

## 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 (5.1).

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 (1.1)	02/15
Dosage and Administration (2.1, 2.4)	02/15
Warnings and Precautions (5.3, 5.4, 5.6, 5.11)	02/15

## INDICATIONS AND USAGE

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

- Multiple myeloma (MM), in combination with dexamethasone (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. Refer to section 14.1 for dexamethasone dosing (2.1, 14.1).
- MDS: 10 mg once daily (2.2).
- MCL: 25 mg once daily orally on Days 1-21 of repeated 28-day cycles (2.3).
- Continue or modify dosing based on clinical and laboratory findings (2.1, 2.2, 2.3).
- Renal impairment: Adjust starting dose 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, 5.8).

## 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).
- Impaired Stem Cell mobilization: A decrease in the number of CD34+ cells collected after treatment (> 4 cycles) with REVLIMID has been reported. Consider early referral to transplant center (5.11).

## ADVERSE REACTIONS

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

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

## DRUG INTERACTIONS

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

## USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Discontinue drug or nursing taking into consideration the importance of the drug to the mother (8.3).
- Patients with Renal Insufficiency: Adjust the starting dose of REVLIMID with moderate or severe renal impairment and on dialysis (2.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

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## 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](http://www.celgeneriskmanagement.com) or by calling the manufacturer’s toll-free number 1-888-423-5436.

#### Hematologic Toxicity (Neutropenia and Thrombocytopenia)

REVLIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q myelodysplastic syndromes had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q myelodysplastic syndromes should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors [see *Dosage and Administration (2.2)*].

#### Venous 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).

### 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

#### **Multiple Myeloma**

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

In patients who are not eligible for autologous stem cell transplantation (ASCT), treatment should continue until disease progression or unacceptable toxicity. For patients who are ASCT-eligible, hematopoietic stem cell mobilization should occur within 4 cycles of a REVLIMID-containing therapy [see *Warnings and Precautions (5.11)*].

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

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

**Table 1: Dose Adjustments for Hematologic Toxicities for MM**

**Platelet counts**

**Thrombocytopenia in MM**

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

**Absolute Neutrophil counts (ANC)**

**Neutropenia in MM**

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

**Other Toxicities in MM**

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

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

[See Dosage and Administration (2.4)].

**2.2 Myelodysplastic Syndromes**

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

**Dose Adjustments for Hematologic Toxicities During MDS Treatment**

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

**Platelet counts**

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

<b>If baseline ≥100,000/mcL</b>	
When Platelets	Recommended Course
Fall to <50,000/mcL	Interrupt REVLIMID treatment
Return to ≥50,000/mcL	Resume REVLIMID at 5 mg daily
<b>If baseline &lt;100,000/mcL</b>	
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
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$<30,000/\text{mcL}$ or $<50,000/\text{mcL}$ with platelet transfusions Return to $\geq 30,000/\text{mcL}$ (without hemostatic failure)	Interrupt REVLIMID treatment
	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**

<b>If baseline ANC <math>\geq 1,000/\text{mcL}</math></b>	
<b>When Neutrophils</b>	<b>Recommended Course</b>
Fall to $<750/\text{mcL}$	Interrupt REVLIMID treatment
Return to $\geq 1,000/\text{mcL}$	Resume REVLIMID at 5 mg daily
<b>If baseline ANC <math>&lt; 1,000/\text{mcL}</math></b>	
<b>When Neutrophils</b>	<b>Recommended Course</b>
Fall to $<500/\text{mcL}$	Interrupt REVLIMID treatment
Return to $\geq 500/\text{mcL}$	Resume REVLIMID at 5 mg daily

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

<b>When Neutrophils</b>	<b>Recommended Course</b>
$<500/\text{mcL}$ for $\geq 7$ days or $<500/\text{mcL}$ associated with fever ( $\geq 38.5^\circ\text{C}$ )	Interrupt REVLIMID treatment
Return to $\geq 500/\text{mcL}$	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**

<b>When Neutrophils</b>	<b>Recommended Course</b>
$<500/\text{mcL}$ for $\geq 7$ days or $<500/\text{mcL}$ associated with fever ( $\geq 38.5^\circ\text{C}$ )	Interrupt REVLIMID treatment
Return to $\geq 500/\text{mcL}$	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  $\leq$  Grade 2.

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

[See Dosage and Administration (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**

<b>When Platelets</b>	<b>Recommended Course</b>
Fall to $<50,000/\text{mcL}$	Interrupt REVLIMID treatment and follow CBC weekly
Return to $\geq 50,000/\text{mcL}$	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**

<b>When Neutrophils</b>	<b>Recommended Course</b>
Fall to $<1000/\text{mcL}$ for at least 7 days	Interrupt REVLIMID treatment and follow

OR Falls to < 1,000/mcL with an associated temperature $\geq 38.5^{\circ}\text{C}$ OR Falls to < 500 /mcL	CBC weekly
Return to $\geq 1,000/\text{mcL}$	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  $\leq$  Grade 2.

#### Starting Dose Adjustment for Renal Impairment in MCL:

[See Dosage and Administration (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  $\text{CLcr} < 60 \text{ mL/min}$ . The recommendations for initial starting doses for patients with MDS or MCL, and MM are as follows:

**Table 2: Starting Dose Adjustments for Patients with Renal Impairment in MDS or MCL**

Category	Renal Function (Cockcroft-Gault)	Dose in MCL	Dose in MDS
<b>Moderate Renal Impairment</b>	$\text{CLcr} 30\text{-}60 \text{ mL/min}$	10 mg Every 24 hours	5 mg Every 24 hours
<b>Severe Renal Impairment</b>	$\text{CLcr} < 30 \text{ mL/min}$ (not requiring dialysis)	15 mg Every 48 hours	2.5 mg Every 24 hours
<b>End Stage Renal Disease</b>	$\text{CLcr} < 30 \text{ mL/min}$ (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.

**Table 3: Starting Dose Adjustments for Patients with Renal Impairment in MM**

Category	Renal Function (Cockcroft-Gault)	Dose in MM
<b>Moderate Renal Impairment</b>	$\text{CLcr} 30\text{-}50 \text{ mL/min}$	10 mg Every 24 hours
<b>Severe Renal Impairment</b>	$\text{CLcr} < 30 \text{ mL/min}$ (not requiring dialysis)	15 mg Every 48 hours
<b>End Stage Renal Disease</b>	$\text{CLcr} < 30 \text{ mL/min}$ (requiring dialysis)	5 mg Once daily. On dialysis days, administer the dose following dialysis.

Moderate renal impairment for MM: Consider escalating the dose to 15 mg after 2 cycles if the patient tolerates the 10 mg dose of lenalidomide without dose-limiting toxicity.

After initiation of REVLIMID therapy, subsequent REVLIMID dose increase or decrease is based on individual patient treatment tolerance, as described elsewhere [See Dosage and Administration (2.1-2.3)].

### 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 (5.8)*].

### 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](http://www.celgeneriskmanagement.com) or by telephone at 1-888-423-5436.

#### 5.3 Hematologic Toxicity

REVLIMID can cause significant neutropenia and thrombocytopenia. Monitor patients with neutropenia for signs of infection. Advise patients to observe for bleeding or bruising, especially with use of concomitant medication that may increase risk of bleeding. Patients taking REVLIMID should have their complete blood counts assessed periodically as described below [see *Dosage and Administration (2.1, 2.2, 2.3)*].

Patients taking REVLIMID in combination with dexamethasone for MM should have their complete blood counts (CBC) assessed every 7 days (weekly) for the first 2 cycles, on Days 1 and 15 of Cycle 3, and every 28 days (4 weeks) thereafter. A dose interruption and/or dose reduction may be required [see *Dosage and Administration (2.1)*].

Patients taking REVLIMID for MDS should have their complete blood counts monitored weekly for the first 8 weeks and at least monthly thereafter. 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)*].

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. 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 after at least one prior therapy 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. In the newly diagnosed multiple myeloma (NDMM) study in which nearly all patients received antithrombotic prophylaxis, DVT was reported as a serious adverse reaction (3.6%, 2.0%, and 1.7%) in the Rd Continuous, Rd18, and MPT Arms, respectively. The frequency of serious adverse reactions of PE was similar between the Rd Continuous, Rd18, and MPT Arms (3.8%, 2.8%, and 3.7%, respectively) [see *Boxed Warning and Adverse Reactions (6.1)*].

Myocardial infarction (1.7%) and stroke (CVA) (2.3%) are increased in patients with multiple myeloma after at least one prior therapy who were treated with REVLIMID and dexamethasone therapy compared to patients treated with placebo and dexamethasone (0.6%, and 0.9%) in clinical trials. In the NDMM study, myocardial infarction (including acute) was reported as a serious adverse reaction (2.3%, 0.6%, and 1.1%) in the Rd Continuous, Rd18, and MPT Arms, respectively. The frequency of serious adverse reactions of CVA was similar between the Rd Continuous, Rd18, and MPT Arms (0.8%, 0.6%, and 0.6%, respectively) [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 2.8 months. In the NDMM study in which nearly all patients received antithrombotic prophylaxis, the overall frequency of thrombotic events was 17.4% in patients in the combined Rd Continuous and Rd18 Arms, and was 11.6% in the MPT Arm. The median time to first thrombosis event was 4.37 months in the combined Rd Continuous and Rd18 Arms. 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 (7.2)*].

#### 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

In clinical trials in patients with multiple myeloma receiving REVLIMID an increase of invasive second primary malignancies notably AML and MDS have been observed. The increase of cases of AML and MDS occurred predominantly in NDMM patients receiving REVLIMID in combination with oral melphalan (frequency of 5.3%) or immediately following high dose intravenous melphalan and ASCT (frequency of up to 5.2%). The frequency of AML and MDS cases in the REVLIMID / dexamethasone arms was observed to be 0.4%. Cases of B-cell malignancies (including Hodgkin's Lymphomas) were observed in clinical trials where patients received lenalidomide in the post-ASCT setting.

Patients who received REVLIMID-containing therapy until disease progression did not show a higher incidence of invasive SPM than patients treated in the fixed duration REVLIMID-containing arms. Monitor patients for the development of second primary malignancies. Take into account both the potential benefit of REVLIMID and the risk of second primary malignancies when considering treatment with REVLIMID.

#### 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.

### 5.11 Impaired Stem Cell Mobilization

A decrease in the number of CD34+ cells collected after treatment (> 4 cycles) with REVLIMID has been reported. In patients who are ASCT candidates, referral to a transplant center should occur early in treatment to optimize the timing of the stem cell collection. In patients who received more than 4 cycles of a REVLIMID-containing treatment or for whom inadequate numbers of CD 34+ cells have been collected with G-CSF alone, G-CSF with cyclophosphamide or the combination of G-CSF with a CXCR4 inhibitor may be considered.

## 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)*]
- Impaired Stem Cell Mobilization [see *Warnings and Precautions (5.11)*]

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

#### Specific Populations

##### ***Newly Diagnosed Multiple Myeloma:***

Data were evaluated from 1613 patients in a large phase 3 study who received at least one dose of REVLIMID with low dose dexamethasone (Rd) given for 2 different durations of time (i.e., until progressive disease [Arm Rd Continuous; N=532] or for up to eighteen 28-day cycles [72 weeks, Arm Rd18; N=540] or who received melphalan, prednisone and thalidomide (Arm MPT; N=541) for a maximum of twelve 42-day cycles (72 weeks). The median treatment duration in the Rd Continuous arm was 80.2 weeks (range 0.7 to 246.7) or 18.4 months (range 0.16 to 56.7).

In general, the most frequently reported adverse reactions were comparable in Arm Rd Continuous and Arm Rd18, and included diarrhea, anemia, constipation, peripheral edema, neutropenia, fatigue, back pain, nausea, asthenia, and insomnia. The most frequently reported Grade 3 or 4 reactions included neutropenia, anemia, thrombocytopenia, pneumonia, asthenia, fatigue, back pain, hypokalemia, rash, cataract, lymphopenia, dyspnea, DVT, hyperglycemia, and leukopenia. The highest frequency of infections occurred in Arm Rd Continuous (75%) compared to Arm MPT (56%). There were more grade 3 and 4 and serious adverse reactions of infection in Arm Rd Continuous than either Arm MPT or Rd18.

In the Rd Continuous arm, the most common adverse reactions leading to dose interruption of REVLIMID were infection events (28.8%); overall, the median time to the first dose interruption of REVLIMID was 7 weeks. The most common adverse reactions leading to dose reduction of REVLIMID in the Rd Continuous arm were hematologic events (10.7%); overall, the median time to the first dose reduction of REVLIMID was 16 weeks. In the Rd Continuous arm, the most common adverse reactions leading to discontinuation of REVLIMID were infection events (3.4%).

In both Rd arms, the frequencies of onset of adverse reactions were generally highest in the first 6 months of treatment and then the frequencies decreased over time or remained stable throughout treatment, except for cataracts. The frequency of onset of cataracts increased over time with 0.7% during the first 6 months and up to 9.6% by the 2nd year of treatment with Rd Continuous.

Table 4 summarizes the adverse reactions reported for the Rd Continuous, Rd18, and MPT treatment arms.

**Table 4: All Adverse Reactions in ≥5.0% and Grade 3/4 Adverse Reactions in ≥ 1.0% of Patients in the Rd Continuous or Rd18 Arms\***

System organ class Preferred term	All Adverse Reactions <sup>a</sup>			Grade 3/4 Adverse Reactions <sup>b</sup>		
	Rd Continuous (N = 532)	Rd18 (N = 540)	MPT (N = 541)	Rd Continuous (N = 532)	Rd18 (N = 540)	MPT (N = 541)
<b>General disorders and administration site conditions</b>						
Fatigue <sup>g</sup>	173 (32.5)	177 (32.8)	154 (28.5)	39 (7.3)	46 (8.5)	31 (5.7)
Asthenia	150 (28.2)	123 (22.8)	124 (22.9)	41 (7.7)	33 (6.1)	32 (5.9)
Pyrexia <sup>c</sup>	114 (21.4)	102 (18.9)	76 (14.0)	13 (2.4)	7 (1.3)	7 (1.3)
Non-cardiac chest pain <sup>f</sup>	29 (5.5)	31 (5.7)	18 (3.3)	<1%	<1%	<1%
<b>Gastrointestinal disorders</b>						
Diarrhea	242 (45.5)	208 (38.5)	89 (16.5)	21 (3.9)	18 (3.3)	8 (1.5)
Abdominal pain <sup>g f</sup>	109 (20.5)	78 (14.4)	60 (11.1)	7 (1.3)	9 (1.7)	<1%
Dyspepsia <sup>f</sup>	57 (10.7)	28 (5.2)	36 (6.7)	<1%	<1%	0 (0.0)
<b>Musculoskeletal and connective tissue disorders</b>						
Back pain <sup>c</sup>	170 (32)	145 (26.9)	116 (21.4)	37 (7)	34 (6.3)	28 (5.2)
Muscle spasms <sup>f</sup>	109 (20.5)	102 (18.9)	61 (11.3)	<1%	<1%	<1%
Arthralgia <sup>f</sup>	101 (19.0)	71 (13.1)	66 (12.2)	9 (1.7)	8 (1.5)	8 (1.5)
Bone pain <sup>f</sup>	87 (16.4)	77 (14.3)	62 (11.5)	16 (3.0)	15 (2.8)	14 (2.6)
Pain in extremity <sup>f</sup>	79 (14.8)	66 (12.2)	61 (11.3)	8 (1.5)	8 (1.5)	7 (1.3)
Musculoskeletal pain <sup>f</sup>	67 (12.6)	59 (10.9)	36 (6.7)	<1%	<1%	<1%
Musculoskeletal chest pain <sup>f</sup>	60 (11.3)	51 (9.4)	39 (7.2)	6 (1.1)	<1%	<1%
Muscular weakness <sup>f</sup>	43 (8.1)	35 (6.5)	29 (5.4)	<1%	8 (1.5)	<1%
Neck pain <sup>f</sup>	40 (7.5)	19 (3.5)	10 (1.8)	<1%	<1%	<1%
<b>Infections and infestations</b>						
Bronchitis <sup>c</sup>	90 (16.9)	59 (10.9)	43 (7.9)	9 (1.7)	6 (1.1)	3 (0.6)
Nasopharyngitis <sup>f</sup>	80 (15)	54 (10)	33 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary tract infection <sup>f</sup>	76 (14.3)	63 (11.7)	41 (7.6)	8 (1.5)	8 (1.5)	<1%
Upper respiratory tract infection <sup>c g f</sup>	69 (13.0)	53 (9.8)	31 (5.7)	<1%	8 (1.5)	<1%
Pneumonia <sup>c g</sup>	93 (17.5)	87 (16.1)	56 (10.4)	60 (11.3)	57 (10.5)	41 (7.6)
Respiratory tract infection <sup>g</sup>	35 (6.6)	25 (4.6)	21 (3.9)	7 (1.3)	4 (0.7)	1 (0.2)
Influenza <sup>f</sup>	33 (6.2)	23 (4.3)	15 (2.8)	<1%	<1%	0 (0.0)
Gastroenteritis <sup>f</sup>	32 (6.0)	17 (3.1)	13 (2.4)	0 (0.0)	<1%	<1%
Lower respiratory tract infection	29 (5.5)	14 (2.6)	16 (3.0)	10 (1.9)	3 (0.6)	3 (0.6)
Rhinitis <sup>f</sup>	29 (5.5)	24 (4.4)	14 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Cellulitis <sup>c</sup>	<5%	<5%	<5%	8 (1.5)	3 (0.6)	2 (0.4)
Sepsis <sup>c g</sup>	33 (6.2)	26 (4.8)	18 (3.3)	26 (4.9)	20 (3.7)	13 (2.4)
<b>Nervous system disorders</b>						
Headache <sup>f</sup>	75 (14.1)	52 (9.6)	56 (10.4)	<1%	<1%	<1%
Dysgeusia <sup>f</sup>	39 (7.3)	45 (8.3)	22 (4.1)	<1%	0 (0.0)	<1%
<b>Blood and lymphatic system disorders<sup>d</sup></b>						
Anemia	233 (43.8)	193 (35.7)	229 (42.3)	97 (18.2)	85 (15.7)	102 (18.9)
Neutropenia	186 (35.0)	178 (33)	328 (60.6)	148 (27.8)	143 (26.5)	243 (44.9)
Thrombocytopenia	104 (19.5)	100 (18.5)	135 (25.0)	44 (8.3)	43 (8.0)	60 (11.1)
Febrile neutropenia	7 (1.3)	17 (3.1)	15 (2.8)	6 (1.1)	16 (3.0)	14 (2.6)
Pancytopenia	5 (0.9)	6 (1.1)	7 (1.3)	1 (0.2)	3 (0.6)	5 (0.9)
<b>Respiratory, thoracic and mediastinal disorders</b>						

System organ class Preferred term	All Adverse Reactions <sup>a</sup>			Grade 3/4 Adverse Reactions <sup>b</sup>		
	Rd Continuous (N = 532)	Rd18 (N = 540)	MPT (N = 541)	Rd Continuous (N = 532)	Rd18 (N = 540)	MPT (N = 541)
Cough <sup>f</sup>	121 (22.7)	94 (17.4)	68 (12.6)	< 1%	< 1%	< 1%
Dyspnea <sup>c,e</sup>	117 (22.0)	89 (16.5)	113 (20.9)	30 (5.6)	22 (4.1)	18 (3.3)
Epistaxis <sup>f</sup>	32 (6.0)	31 (5.7)	17 (3.1)	< 1%	< 1%	0 (0.0)
Oropharyngeal pain <sup>f</sup>	30 (5.6)	22 (4.1)	14 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnea exertional <sup>e</sup>	27 (5.1)	29 (5.4)	< 5%	6 (1.1)	2 (0.4)	0 (0.0)
<b>Metabolism and nutrition disorders</b>						
Decreased appetite	123 (23.1)	115 (21.3)	72 (13.3)	14 (2.6)	7 (1.3)	5 (0.9)
Hypokalemia <sup>g</sup>	91 (17.1)	62 (11.5)	38 (7)	35 (6.6)	20 (3.7)	11 (2.0)
Hyperglycemia	62 (11.7)	52 (9.6)	19 (3.5)	28 (5.3)	23 (4.3)	9 (1.7)
Hypocalcemia	57 (10.7)	56 (10.4)	31 (5.7)	23 (4.3)	19 (3.5)	8 (1.5)
Dehydration <sup>g</sup>	25 (4.7)	29 (5.4)	17 (3.1)	8 (1.5)	13 (2.4)	9 (1.7)
Gout <sup>e</sup>	< 5%	< 5%	< 5%	8 (1.5)	0 (0.0)	0 (0.0)
Diabetes mellitus <sup>g,e</sup>	< 5%	< 5%	< 5%	8 (1.5)	4 (0.7)	2 (0.4)
Hypophosphatemia <sup>e</sup>	< 5%	< 5%	< 5%	7 (1.3)	3 (0.6)	1 (0.2)
Hyponatremia <sup>g,e</sup>	< 5%	< 5%	< 5%	7 (1.3)	13 (2.4)	6 (1.1)
<b>Skin and subcutaneous tissue disorders</b>						
Rash	139 (26.1)	151 (28.0)	105 (19.4)	39 (7.3)	38 (7.0)	33 (6.1)
Pruritus <sup>f</sup>	47 (8.8)	49 (9.1)	24 (4.4)	< 1%	< 1%	< 1%
<b>Psychiatric disorders</b>						
Insomnia	147 (27.6)	127 (23.5)	53 (9.8)	4 (0.8)	6 (1.1)	0 (0.0)
Depression	58 (10.9)	46 (8.5)	30 (5.5)	10 (1.9)	4 (0.7)	1 (0.2)
<b>Vascular disorders</b>						
Deep vein thrombosis <sup>c,g</sup>	55 (10.3)	39 (7.2)	22 (4.1)	30 (5.6)	20 (3.7)	15 (2.8)
Hypotension <sup>c,g</sup>	51 (9.6)	35 (6.5)	36 (6.7)	11 (2.1)	8 (1.5)	6 (1.1)
<b>Injury, Poisoning, and Procedural Complications</b>						
Fall <sup>f</sup>	43 (8.1)	25 (4.6)	25 (4.6)	< 1%	6 (1.1)	6 (1.1)
Contusion <sup>f</sup>	33 (6.2)	24 (4.4)	15 (2.8)	< 1%	< 1%	0 (0.0)
<b>Eye disorders</b>						
Cataract	73 (13.7)	31 (5.7)	5 (0.9)	31 (5.8)	14 (2.6)	3 (0.6)
Cataract subcapsular <sup>e</sup>	< 5%	< 5%	< 5%	7 (1.3)	0 (0.0)	0 (0.0)
<b>Investigations</b>						
Weight decreased	72 (13.5)	78 (14.4)	48 (8.9)	11 (2.1)	4 (0.7)	4 (0.7)
<b>Cardiac disorders</b>						
Atrial fibrillation <sup>c</sup>	37 (7.0)	25 (4.6)	25 (4.6)	13 (2.4)	9 (1.7)	6 (1.1)
Myocardial infarction (including acute) <sup>c,e</sup>	< 5%	< 5%	< 5%	10 (1.9)	3 (0.6)	5 (0.9)
<b>Renal and Urinary disorders</b>						
Renal failure (including acute) <sup>c,f</sup>	49 (9.2)	54 (10.0)	37 (6.8)	28 (5.3)	33 (6.1)	29 (5.4)
<b>Neoplasms benign, malignant and unspecified (Incl cysts and polyps)</b>						
Squamous cell carcinoma <sup>c,e</sup>	< 5%	< 5%	< 5%	8 (1.5)	4 (0.7)	0 (0.0)
Basal cell carcinoma <sup>c,e,f</sup>	< 5%	< 5%	< 5%	< 1%	< 1%	0 (0.0)

Note: System organ classes (SOC) and preferred terms (PTs) reflect coding of adverse reactions using MedDRA. A subject with multiple occurrences of an adverse reaction is counted only once under the applicable SOC/PT.

<sup>a</sup> All treatment-emergent adverse reactions in at least 5.0% of subjects in the Rd Continuous or Rd18 Arms and at least a 2.0% higher frequency (%) in either the Rd Continuous or Rd18 Arms compared to the MPT Arm.

<sup>b</sup> All grade 3 or 4 treatment-emergent adverse reactions in at least 1.0% of subjects in the Rd Continuous or Rd18 Arms and at least a 1.0% higher frequency (%) in either the Rd Continuous or Rd18 Arms compared to the MPT Arm.

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

<sup>d</sup> Preferred terms for the blood and lymphatic system disorders SOC were included by medical judgment as known adverse reactions for Rd Continuous/Rd18, and have also been reported as serious.

<sup>e</sup> Footnote “a” not applicable

<sup>f</sup> Footnote “b” not applicable.

<sup>@</sup> - adverse reactions in which at least one resulted in a fatal outcome

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

\*PTs for combined adverse reaction terms:

Abdominal Pain: Abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain

Pneumonias: Pneumonia, lobar pneumonia, pneumonia pneumococcal, bronchopneumonia, pneumocystis jiroveci pneumonia, pneumonia legionella, pneumonia staphylococcal, pneumonia klebsiella, atypical pneumonia, pneumonia bacterial, pneumonia escherichia, pneumonia streptococcal, pneumonia viral

Sepsis: Sepsis, septic shock, urosepsis, escherichia sepsis, neutropenic sepsis, pneumococcal sepsis, staphylococcal sepsis, bacterial sepsis, meningococcal sepsis, enterococcal sepsis, klebsiella sepsis, pseudomonal sepsis

Rash: Rash, rash pruritic, rash erythematous, rash maculo-papular, rash generalised, rash papular, exfoliative rash, rash follicular, rash macular, drug rash with eosinophilia and systemic symptoms, erythema multiforme, rash pustular

Deep Vein Thrombosis: Deep vein thrombosis, venous thrombosis limb, venous thrombosis

#### **After At Least One Prior Therapy for MM**

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 reactions and Grade 3/4 adverse reactions were more frequent in patients who received the combination of REVLIMID/dexamethasone compared to placebo/dexamethasone.

Tables 5, 6, and 7 summarize the adverse reactions reported for REVLIMID/dexamethasone and placebo/dexamethasone groups.

**Table 5: 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 (%)
<b>Blood and lymphatic system disorders</b>		
Neutropenia <sup>%</sup>	149 (42.2)	22 (6.3)
Anemia <sup>@</sup>	111 (31.4)	83 (23.7)
Thrombocytopenia <sup>@</sup>	76 (21.5)	37 (10.6)
Leukopenia	28 (7.9)	4 (1.1)
Lymphopenia	19 (5.4)	5 (1.4)
<b>General disorders and administration site conditions</b>		
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)
<b>Gastrointestinal disorders</b>		
Constipation	143 (40.5)	74 (21.1)
Diarrhea <sup>@</sup>	136 (38.5)	96 (27.4)
Nausea <sup>@</sup>	92 (26.1)	75 (21.4)
Vomiting <sup>@</sup>	43 (12.2)	33 (9.4)

System Organ Class/ Preferred Term	REVLIMID/Dex* (N=353) n (%)	Placebo/Dex * (N=350) n (%)
Abdominal Pain <sup>®</sup>	35 (9.9)	22 (6.3)
Dry Mouth	25 (7.1)	13 (3.7)
<b>Musculoskeletal and connective tissue disorders</b>		
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)
<b>Nervous system disorders</b>		
Dizziness	82 (23.2)	59 (16.9)
Tremor	75 (21.2)	26 (7.4)
Dysgeusia	54 (15.3)	34 (9.7)
Hypoaesthesia	36 (10.2)	25 (7.1)
Neuropathy <sup>a</sup>	23 (6.5)	13 (3.7)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
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)
<b>Infections<sup>b</sup> and infestations</b>		
Upper respiratory tract infection	87 (24.6)	55 (15.7)
Pneumonia <sup>®</sup>	48 (13.6)	29 (8.3)
Urinary Tract Infection	30 (8.5)	19 (5.4)
Sinusitis	26 (7.4)	16 (4.6)
<b>Skin and subcutaneous system disorders</b>		
Rash <sup>c</sup>	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)
<b>Metabolism and nutrition disorders</b>		
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)
Hypomagnesemia	24 (6.8)	10 (2.9)
<b>Investigations</b>		
Weight Decreased	69 (19.5)	52 (14.9)
<b>Eye disorders</b>		
Blurred vision	61 (17.3)	40 (11.4)
<b>Vascular disorders</b>		
Deep vein thrombosis <sup>®</sup>	33 (9.3)	15 (4.3)
Hypertension	28 (7.9)	20 (5.7)
Hypotension	25 (7.1)	15 (4.3)

**Table 6: 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 <sup>#</sup> (N=353) n (%)	Placebo/Dex <sup>#</sup> (N=350) n (%)
<b>Blood and lymphatic system disorders</b>		
Neutropenia <sup>®</sup>	118 (33.4)	12 (3.4)
Thrombocytopenia <sup>®</sup>	43 (12.2)	22 (6.3)
Anemia <sup>®</sup>	35 (9.9)	20 (5.7)
Leukopenia	14 (4.0)	1 (0.3)
Lymphopenia	10 (2.8)	4 (1.1)
Febrile Neutropenia <sup>®</sup>	8 (2.3)	0 (0.0)
<b>General disorders and administration site conditions</b>		
Fatigue	23 (6.5)	17 (4.9)
<b>Vascular disorders</b>		
Deep vein thrombosis <sup>®</sup>	29 (8.2)	12 (3.4)
<b>Infections and infestations</b>		
Pneumonia <sup>®</sup>	30 (8.5)	19 (5.4)
Urinary Tract Infection	5 (1.4)	1 (0.3)
<b>Metabolism and nutrition disorders</b>		
Hypokalemia	17 (4.8)	5 (1.4)
Hypocalcemia	13 (3.7)	6 (1.7)
Hypophosphatemia	9 (2.5)	0 (0.0)
<b>Respiratory, thoracic and mediastinal disorders</b>		
Pulmonary embolism <sup>®</sup>	14 (4.0)	3 (0.9)
Respiratory Distress <sup>®</sup>	4 (1.1)	0 (0.0)
<b>Musculoskeletal and connective tissue disorders</b>		
Muscle weakness	20 (5.7)	10 (2.9)
<b>Gastrointestinal disorders</b>		
Diarrhea <sup>®</sup>	11 (3.1)	4 (1.1)
Constipation	7 (2.0)	1 (0.3)
Nausea <sup>®</sup>	6 (1.7)	2 (0.6)
<b>Cardiac disorders</b>		
Atrial fibrillation <sup>®</sup>	13 (3.7)	4 (1.1)
Tachycardia	6 (1.7)	1 (0.3)
Cardiac Failure Congestive <sup>®</sup>	5 (1.4)	1 (0.3)
<b>Nervous System disorders</b>		
Syncope	10 (2.8)	3 (0.9)
Dizziness	7 (2.0)	3 (0.9)
<b>Eye Disorders</b>		
Cataract	6 (1.7)	1 (0.3)
Cataract Unilateral	5 (1.4)	0 (0.0)
<b>Psychiatric Disorder</b>		
Depression	10 (2.8)	6 (1.7)

**Table 7: 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 <sup>®</sup> (N=353) n (%)	Placebo/Dex <sup>®</sup> (N=350) n (%)
<b>Blood and lymphatic system disorders</b>		

System Organ Class/ Preferred Term	REVLIMID/Dex <sup>®</sup> (N=353) n (%)	Placebo/Dex <sup>®</sup> (N=350) n (%)
Febrile Neutropenia <sup>®</sup>	6 (1.7)	0 (0.0)
<b>Vascular disorders</b>		
Deep vein thrombosis <sup>®</sup>	26 (7.4)	11 (3.1)
<b>Infections and infestations</b>		
Pneumonia <sup>®</sup>	33 (9.3)	21 (6.0)
<b>Respiratory, thoracic, and mediastinal disorders</b>		
Pulmonary embolism <sup>®</sup>	13 (3.7)	3 (0.9)
<b>Cardiac disorders</b>		
Atrial fibrillation <sup>®</sup>	11 (3.1)	2 (0.6)
Cardiac Failure Congestive <sup>®</sup>	5 (1.4)	0 (0.0)
<b>Nervous system disorders</b>		
Cerebrovascular accident <sup>®</sup>	7 (2.0)	3 (0.9)
<b>Gastrointestinal disorders</b>		
Diarrhea <sup>®</sup>	6 (1.7)	2 (0.6)
<b>Musculoskeletal and connective tissue disorders</b>		
Bone Pain	4 (1.1)	0 (0.0)

For Tables 5, 6 and 7 above:

<sup>®</sup> - adverse reactions in which at least one resulted in a fatal outcome

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

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 reactions 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 in the 2 studies in patients with at least 1 prior therapy with discontinuations due to DVT adverse reactions reported at comparable rates between groups. In the NDMM study, DVT was reported as an adverse reaction (all grades: 10.3%, 7.2%, 4.1%), as a serious adverse reaction (3.6%, 2.0%, 1.7%), and as a Grade 3/4 adverse reaction (5.6%, 3.7%, 2.8%) in the Rd Continuous, Rd18, and MPT Arms, respectively. Discontinuations and dose reductions due to DVT adverse reactions were reported at comparable rates between the Rd Continuous and Rd18 Arms (both <1%). Interruption of REVLIMID treatment due to DVT adverse reactions was reported at comparable rates between the Rd Continuous (2.3%) and Rd18 (1.5%) arms.

Pulmonary embolism (PE) was reported as a serious adverse drug reaction (3.7%) or Grade 3/4 (4.0%) at a higher rate in the REVLIMID/dexamethasone group compared to 0.9% (serious or grade 3/4) in the placebo/dexamethasone group in the 2 studies in patients with, at least 1 prior therapy, with discontinuations due to PE adverse reactions reported at comparable rates between groups. In the NDMM study, the frequency of adverse reactions of PE was similar between the Rd Continuous, Rd18, and MPT Arms for adverse reactions (all grades: 3.9%, 3.3%, and 4.3%, respectively), serious adverse reactions (3.8%, 2.8%, and 3.7%, respectively), and grade 3/4 adverse reactions (3.8%, 3.0%, and 3.7%, respectively).

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. In the NDMM study, myocardial infarction (including acute) was reported as an adverse reaction (all grades: 2.4%, 0.6%, and 1.1%), as a serious adverse reaction, (2.3%, 0.6%, and 1.1%), or as a severe adverse reaction (1.9%, 0.6%, and 0.9%) in the Rd Continuous, Rd18, and MPT Arms, respectively.

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. In the NDMM study, CVA was reported as an adverse reaction (all grades: 0.8%, 0.6%, and 0.6%), as a serious adverse reaction (0.8%, 0.6 %, and 0.6%), or as a severe adverse reaction (0.6%, 0.6%, 0.2%) in the Rd Continuous, Rd18, and MPT arms respectively.

#### **Other Adverse Reactions: After At Least One Prior Therapy for MM**

In these 2 studies, 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

***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 8 summarizes the adverse events that were reported in  $\geq 5\%$  of the REVLIMID treated patients in the del 5q MDS clinical study. Table 9 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 8: Summary of Adverse Events Reported in  $\geq 5\%$  of the REVLIMID Treated Patients in del 5q MDS Clinical Study**

System organ class/Preferred term <sup>[a]</sup>	10 mg Overall (N=148)	
Patients with at least one adverse event	148	(100.0)
<b>Blood and Lymphatic System Disorders</b>		
Thrombocytopenia	91	(61.5)
Neutropenia	87	(58.8)
Anemia	17	(11.5)
Leukopenia	12	(8.1)
Febrile Neutropenia	8	(5.4)
<b>Skin and Subcutaneous Tissue Disorders</b>		
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)
<b>Gastrointestinal Disorders</b>		
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)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
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)
<b>General Disorders and Administration Site Conditions</b>		
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)
<b>Musculoskeletal and Connective Tissue Disorders</b>		
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)
<b>Nervous System Disorders</b>		
Dizziness	29	(19.6)
Headache	29	(19.6)
Hypoesthesia	10	(6.8)
Dysgeusia	9	(6.1)
Peripheral Neuropathy	8	(5.4)
<b>Infections and Infestations</b>		
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)
<b>Metabolism and Nutrition Disorders</b>		
Hypokalemia	16	(10.8)
Anorexia	15	(10.1)

Hypomagnesemia	9	(6.1)
<b>Investigations</b>		
Alanine Aminotransferase Increased	12	(8.1)
<b>Psychiatric Disorders</b>		
Insomnia	15	(10.1)
Depression	8	(5.4)
<b>Renal and Urinary Disorders</b>		
Dysuria	10	(6.8)
<b>Vascular Disorders</b>		
Hypertension	9	(6.1)
<b>Endocrine Disorders</b>		
Acquired Hypothyroidism	10	(6.8)
<b>Cardiac Disorders</b>		
Palpitations	8	(5.4)

<sup>[a]</sup> 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 9: Most Frequently Observed Grade 3 and 4 Adverse Events [1]  
Regardless of Relationship to Study Drug Treatment**

Preferred term <sup>[2]</sup>	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)

<sup>[1]</sup> Adverse events with frequency  $\geq 1\%$  in the 10 mg Overall group. Grade 3 and 4 are based on National Cancer Institute Common Toxicity Criteria version 2.

<sup>[2]</sup> 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 8 or 9 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, hyponatremia, 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

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

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

<sup>1</sup>-MCL trial AEs – All treatment emergent AEs with ≥10% of subjects

<sup>2</sup>-MCL trial Grade 3/4 AEs – All treatment-emergent Grade 3/4 AEs in 2 or more subjects

<sup>§</sup>-MCL trial Serious AEs – All treatment-emergent SAEs in 2 or more subjects

<sup>@</sup> - AEs where at least one resulted in a fatal outcome

<sup>%</sup> - 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)

<sup>#</sup> - All PTs under SOC of Infections except for rare infections of Public Health interest will be considered listed

<sup>+</sup> - 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:** Dysgeusia, 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 (including cysts and polyps):** Basal cell carcinoma  
**Cardiac Disorder:** Supraventricular tachycardia

## 6.2 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 (5.7 to 5.10)*].

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.

### 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 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)*].

### 7.3 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.

## 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 91 years of age.

After At Least One Prior Therapy: 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.

NDMM: Overall, of the 1613 patients in the NDMM study who received study treatment, 94% (1521/1613) were 65 years of age or older, while 35% (561/1613) were over 75 years of age. The percentage of patients over age 75 was similar between study arms (Rd Continuous: 33%; Rd18: 34%; MPT: 33%). Overall, across all treatment arms, the frequency in most of the AE categories (eg, all AEs, grade 3/4 AEs, serious AEs) was higher in older (> 75 years of age) than in younger (≤ 75 years of age) subjects. Grade 3 or 4 AEs in the General Disorders and Administration Site Conditions SOC were consistently reported at a higher frequency (with a difference of at least 5%) in older subjects than in younger subjects across all treatment arms. Grade 3 or 4 TEAEs in the Infections and Infestations, Cardiac Disorders (including cardiac failure and congestive cardiac failure), Skin and Subcutaneous Tissue Disorders, and Renal and Urinary Disorders (including renal failure) SOCs were also reported slightly, but consistently, more frequently (<5% difference), in older subjects than in younger subjects across all treatment arms. For other SOCs (e.g., Blood and Lymphatic System Disorders, Infections and Infestations, Cardiac Disorders, Vascular Disorders), there was a less consistent trend for increased frequency of grade 3/4 AEs in older vs younger subjects across all treatment arms. Serious AEs were generally reported at a higher frequency in the older subjects than in the younger subjects across all treatment arms.

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 (CL<sub>Cr</sub> 30-60 mL/min) or severe renal impairment (CL<sub>Cr</sub> < 30 mL/min) and in patients on dialysis [see *Dosage and Administration* (2.4)].

### 8.8 Hepatic Impairment

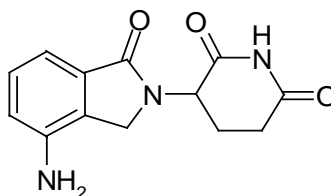
No dedicated study has been conducted in patients with hepatic impairment. The elimination of unchanged lenalidomide is predominantly by the renal route.

## 10 OVERDOSAGE

There is no specific experience in the management of lenalidomide overdose in patients with MM, MDS, or MCL. In dose-ranging studies in healthy subjects, some were exposed to up to 200 mg (administered 100 mg BID) and in single-dose studies, some subjects were exposed to up to 400 mg. Pruritus, urticaria, rash, and elevated liver transaminases were the primary reported AEs. In clinical trials, the dose-limiting toxicity was neutropenia and thrombocytopenia.

## 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-2H-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:



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

The empirical formula for lenalidomide is C<sub>13</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub>, 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- $\alpha$  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 ( $CL_{Cr} \geq 60$  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%.

Lenalidomide is present in semen at 2 hours (1379 ng/ejaculate) and 24 hours (35 ng/ejaculate) after the administration of REVLIMID 25 mg daily.

#### Metabolism

Lenalidomide undergoes limited metabolism. Unchanged lenalidomide is the predominant circulating component in humans. Two identified metabolites are 5-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.

#### Drug Interactions

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).

*In vitro*, lenalidomide is a substrate, but is not an inhibitor of P-glycoprotein (P-gp). In healthy volunteers, co-administration of REVLIMID (25 mg) after multiple doses of a P-gp inhibitor such as quinidine (600 mg twice daily) does not result in a clinically significant increase in the  $C_{max}$  and AUC of REVLIMID. In healthy volunteers, co-administration of the P-gp inhibitor/substrate, temsirolimus (25 mg), with REVLIMID (25 mg) does not significantly alter the pharmacokinetics of REVLIMID, temsirolimus, or its metabolite, sirolimus.

*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. Lenalidomide is not an inhibitor of bile salt export pump (BSEP), BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2. Lenalidomide does not inhibit bilirubin glucuronidation formation in human liver microsomes with UGT1A1 genotyped as UGT1A1\*1/\*1, UGT1A1\*1/\*28, and UGT1A1\*28/\*28.

#### 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 30% of the drug in body was removed during a 4-hour hemodialysis 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**

#### ***Randomized, Open-Label Clinical Trial in Patients with Newly Diagnosed Multiple Myeloma:***

A randomized multicenter, open-label, 3-arm trial of 1,623 patients, was conducted to compare the efficacy and safety of REVLIMID and low-dose dexamethasone (Rd) given for 2 different durations of time to that of melphalan, prednisone and thalidomide (MPT) in newly diagnosed multiple myeloma patients who were not a candidate for stem cell transplant. In the first arm of the study, Rd was given continuously until progressive disease [Arm Rd Continuous]. In the second arm, Rd was given for up to eighteen 28-day cycles [72 weeks, Arm Rd18]. In the third arm, melphalan, prednisone and thalidomide (MPT) was given for a maximum of twelve 42-day cycles (72 weeks). For the purposes of this study, a patient who was < 65 years of age was not a candidate for SCT if the patient refused to undergo SCT therapy or the patient did not have access to SCT due to cost or other reasons. Patients were stratified at randomization by age (≤75 versus >75 years), stage (ISS Stages I and II versus Stage III), and country.

Patients in the Rd Continuous and Rd18 arms received REVLIMID 25 mg once daily on Days 1 to 21 of 28-day cycles. Dexamethasone was dosed 40 mg once daily on Days 1, 8, 15, and 22 of each 28-day cycle. For patients over > 75 years old, the starting dose of dexamethasone was 20 mg orally once daily on days 1,8,15, and 22 of repeated 28-day cycles. Initial dose and regimens for Rd Continuous and Rd18 were adjusted according to age and renal function. All patients received prophylactic anticoagulation with the most commonly used being aspirin.

The demographics and disease-related baseline characteristics of the patients were balanced among the 3 arms. In general, study subjects had advanced-stage disease. Of the total study population, the median age was 73 in the 3 arms with 35% of total patients > 75 years of age; 59% had ISS Stage I/II; 41% had ISS stage III; 9% had severe renal impairment (creatinine clearance [CLcr] < 30 mL/min); 23% had moderate renal impairment (CLcr > 30 to 50 mL/min); 44% had mild renal impairment (CLcr > 50 to 80 mL/min). For ECOG Performance Status, 29% were Grade 0, 49% Grade 1, 21% Grade 2, 0.4% ≥ Grade 3.

The primary efficacy endpoint, PFS, was defined as the time from randomization to the first documentation of disease progression as determined by Independent Response Adjudication Committee (IRAC), based on International Myeloma Working Group [IMWG] criteria or death due to any cause, whichever occurred first during the study until the end of the PFS follow-up phase. For the efficacy analysis of all endpoints, the primary comparison was between Rd Continuous and MPT arms. The efficacy results are summarized in the table below. PFS was significantly longer with Rd Continuous than MPT: HR 0.72 (95% CI: 0.61-0.85 p <0.0001). A lower percentage of subjects in the Rd Continuous arm compared with the MPT arm had PFS events (52% versus 61%, respectively). The improvement in median PFS time in the Rd Continuous arm compared with the MPT arm was 4.3 months. The myeloma response rate was higher with Rd Continuous compared with MPT (75.1% versus 62.3%); with a complete response in 15.1% of Rd Continuous arm patients versus 9.3% in the MPT arm. The median time to first response was 1.8 months in the Rd Continuous arm versus 2.8 months in the MPT arm.

For the interim OS analysis with 03 March 2014 data cutoff, the median follow-up time for all surviving patients is 45.5 months, with 697 death events, representing 78% of prespecified events required for the planned final OS analysis (697/896 of the final OS events). The observed OS HR was 0.75 for Rd Continuous versus MPT (95% CI = 0.62, 0.90).

Table 11: Overview of Efficacy Results – Study MM-020 (Intent-to-treat Population)

	<b>Rd Continuous (N = 535)</b>	<b>Rd18 (N = 541)</b>	<b>MPT (N = 547)</b>
<b>PFS – IRAC (months)<sup>g</sup></b>			
Number of PFS events	278 (52.0)	348 (64.3)	334 (61.1)
Median <sup>a</sup> PFS time, months (95% CI) <sup>b</sup>	25.5 (20.7, 29.4)	20.7 (19.4, 22.0)	21.2 (19.3, 23.2)
HR [95% CI] <sup>c</sup> ; p-value <sup>d</sup>			
Rd Continuous vs MPT	0.72 (0.61, 0.85); <0.0001		
Rd Continuous vs Rd18	0.70 (0.60, 0.82)		
Rd18 vs MPT	1.03 (0.89, 1.20)		
<b>Overall Survival (months)<sup>h</sup></b>			
Number of Death events	208 (38.9)	228 (42.1)	261 (47.7)
Median <sup>a</sup> OS time, months (95% CI) <sup>b</sup>	58.9 (56.0, NE) <sup>f</sup>	56.7 (50.1, NE)	48.5 (44.2, 52.0)
HR [95% CI] <sup>c</sup>			
Rd Continuous vs MPT	0.75 (0.62, 0.90)		
Rd Continuous vs Rd18	0.91 (0.75, 1.09)		
Rd18 vs MPT	0.83 (0.69, 0.99)		
<b>Response Rate<sup>e</sup> – IRAC, n (%)<sup>g</sup></b>			
CR	81 (15.1)	77 (14.2)	51 (9.3)
VGPR	152 (28.4)	154 (28.5)	103 (18.8)
PR	169 (31.6)	166 (30.7)	187 (34.2)
Overall response: CR, VGPR, or PR	402 (75.1)	397 (73.4)	341 (62.3)

CR = complete response; d = low-dose dexamethasone; HR = hazard ratio; IRAC = Independent Response Adjudication Committee; M = melphalan; NE = not estimable; OS = overall survival; P = prednisone; PFS = progression-free survival; PR = partial response; R = lenalidomide; Rd Continuous = Rd given until documentation of progressive disease; Rd18 = Rd given for ≤ 18 cycles; T = thalidomide; VGPR = very good partial response; vs = versus.

<sup>a</sup> The median is based on the Kaplan-Meier estimate.

<sup>b</sup> The 95% Confidence Interval (CI) about the median.

<sup>c</sup> Based on Cox proportional hazards model comparing the hazard functions associated with the indicated treatment arms.

<sup>d</sup> The p-value is based on the unstratified log-rank test of Kaplan-Meier curve differences between the indicated treatment arms.

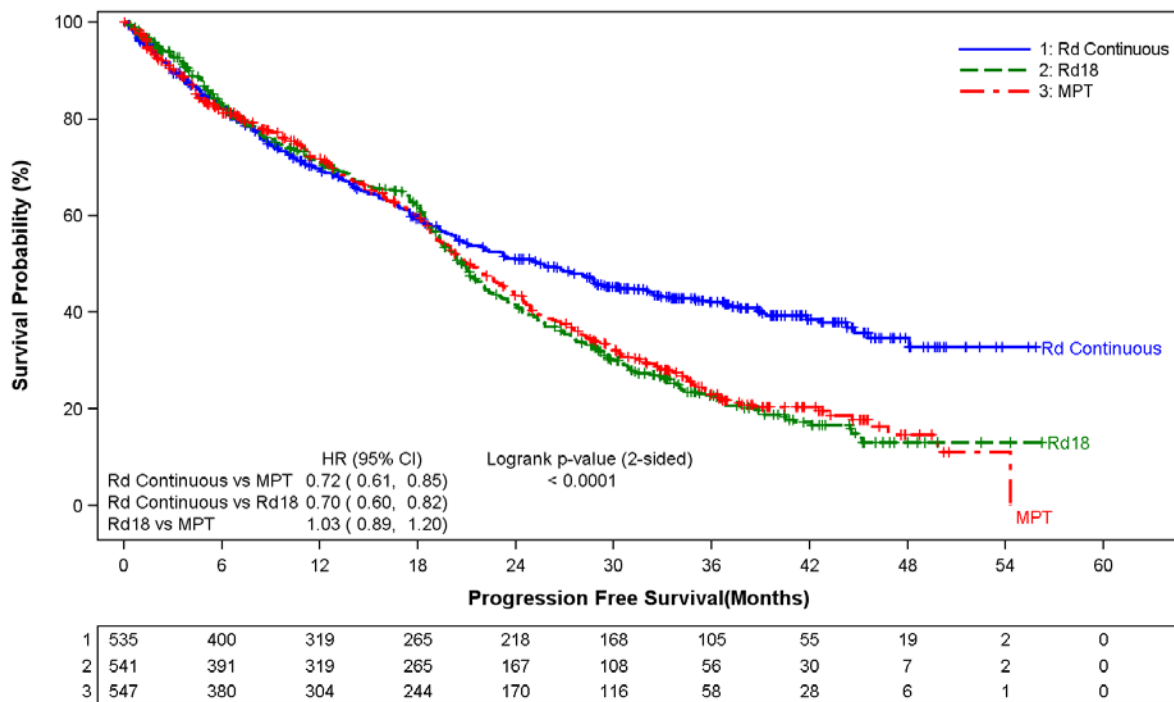
<sup>e</sup> Best assessment of response during the treatment phase of the study

<sup>f</sup> Including patients with no response assessment data or whose only assessment was “response not evaluable.”

<sup>g</sup> Data cutoff date = 24 May 2013.

<sup>h</sup> Data cutoff date = 3 March 2014.

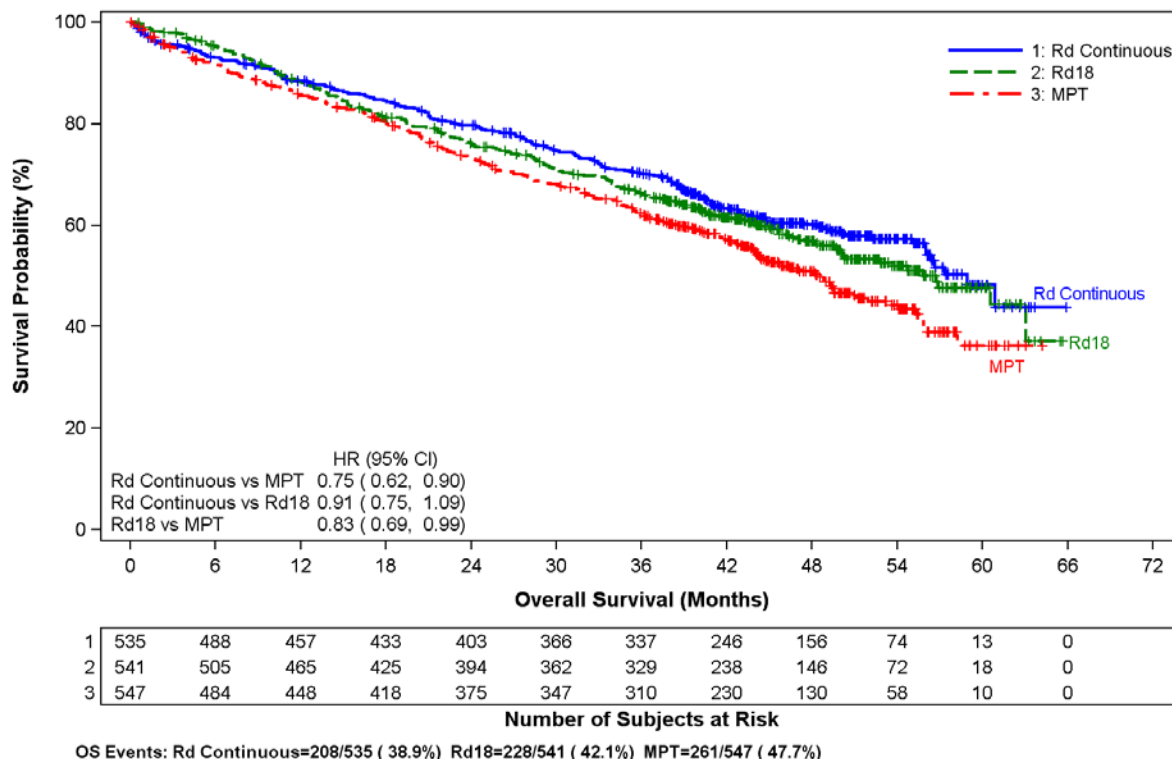
**Kaplan-Meier Curves of Progression-free Survival Based on IRAC Assessment (ITT Population)  
 Between Arms Rd Continuous, Rd18 and MPT  
 Cutoff date: 24 May 2013**



**PFS Events: Rd Continuous=278/535 ( 52.0%) Rd18=348/541 ( 64.3%) MPT=334/547 ( 61.1%)**

CI = confidence interval; d = low-dose dexamethasone; HR = hazard ratio; IRAC = Independent Response Adjudication Committee;  
 M = melphalan; P = prednisone; R = lenalidomide; Rd Continuous = Rd given until documentation of progressive disease; Rd18 = Rd given for ≤ 18 cycles; T = thalidomide.

**Kaplan-Meier Curves of Overall Survival (ITT Population)  
Between Arms Rd Continuous, Rd18 and MPT  
Cutoff date: 03 Mar 2014**



CI = confidence interval; d = low-dose dexamethasone; HR = hazard ratio; M = melphalan; P = prednisone; R = lenalidomide; Rd Continuous = Rd given until documentation of progressive disease; Rd18 = Rd given for ≤18 cycles; T = thalidomide.

**Randomized, Open-Label Clinical Studies in Patients with Previously Treated 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) ≥ 1000/mm<sup>3</sup>, platelet counts ≥ 75,000/mm<sup>3</sup>, 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 12 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 12: 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
<b>Patient Characteristics</b>				
Age (years)				
Median	64	62	63	64
Min, Max	36, 86	37, 85	33, 84	40, 82
Sex				
Male	106 (60%)	104 (59%)	104 (59%)	103 (59%)
Female	71 (40%)	72 (41%)	72 (41%)	72 (41%)
Race/Ethnicity				
White	141(80%)	148 (84%)	172 (98%)	175(100%)
Other	36 (20%)	28 (16%)	4 (2%)	0 (0%)
ECOG Performance				
Status 0-1	157 (89%)	168 (95%)	150 (85%)	144 (82%)
<b>Disease Characteristics</b>				
Multiple Myeloma Stage (Durie-Salmon)				
I	3%	3%	6%	5%
II	32%	31%	28%	33%
III	64%	66%	65%	63%
B2-microglobulin (mg/L)				
≤ 2.5 mg/L	52 (29%)	51 (29%)	51 (29%)	48 (27%)
> 2.5 mg/L	125 (71%)	125 (71%)	125 (71%)	127 (73%)
<b>Number of Prior Therapies</b>				
1	38%	38%	32%	33%
≥ 2	62%	62%	68%	67%
<b>Types of Prior Therapies</b>				
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 13: 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
<b>TTP</b>				
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 <sup>s</sup>	<0.001		<0.001	
<b>Response</b>				
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

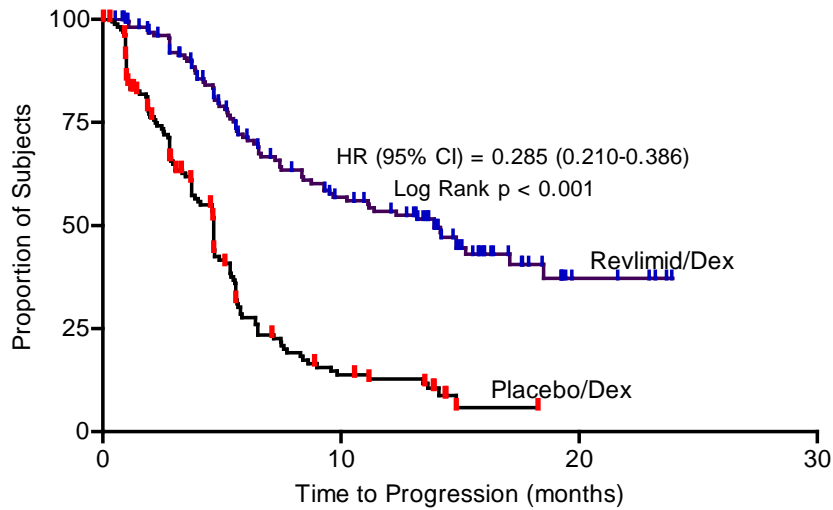
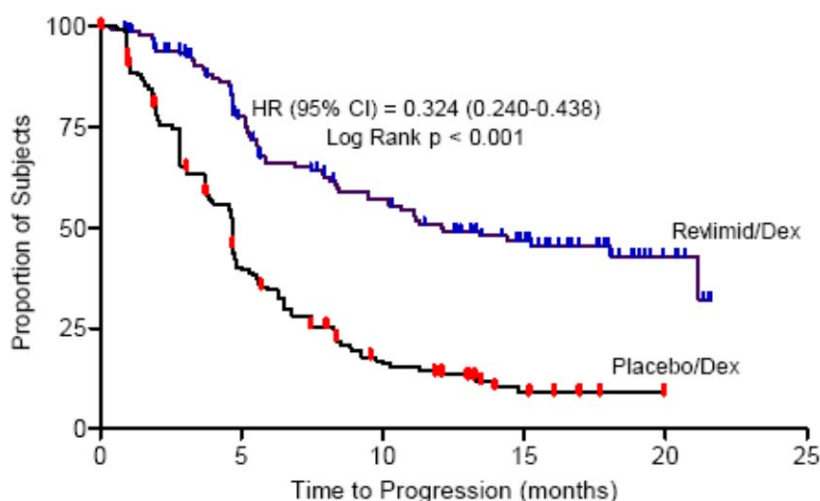


Figure 2: Kaplan-Meier Estimate of Time to Progression — Study 2



#### 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  $\geq 2$  units of RBCs within 8 weeks prior to study treatment. The study enrolled patients with absolute neutrophil counts (ANC)  $\geq 500/\text{mm}^3$ , platelet counts  $\geq 50,000/\text{mm}^3$ , serum creatinine  $\leq 2.5$  mg/dL, serum SGOT/AST or SGPT/ALT  $\leq 3$  x upper limit of normal (ULN), and serum direct bilirubin  $\leq 2$  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 14.

Table 14: Baseline Demographic and Disease-Related Characteristics in the MDS Study

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

<sup>[a]</sup> 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  $\geq$  2.5); Combined score = (Marrow blast score + Karyotype score + Cytopenia score)

<sup>[b]</sup> 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  $\geq$ 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  $\geq$ 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)  $\geq$ 1500/ mm<sup>3</sup>, platelet counts  $\geq$  60,000/mm<sup>3</sup>, serum SGOT/AST or SGPT/ALT  $\leq$ 3x upper limit of normal (ULN) unless there was documented evidence of liver involvement by lymphoma, serum total bilirubin  $\leq$ 1.5 x ULN except in cases of Gilbert’s syndrome or documented liver involvement by lymphoma, and calculated creatinine clearance (Cockcroft-Gault formula)  $\geq$ 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 15: 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)
<b>ECOG Performance Status<sup>a</sup> n (%)</b>	
0	43 (32)
1	73 (54)
2	17 (13)
3	1 (<1)
<b>Advanced MCL Stage, n (%)</b>	
III	27 (20)
IV	97 (72)
<b>High or Intermediate MIPI Score<sup>b</sup>, n (%)</b>	90 (67)
<b>High Tumor Burden<sup>c</sup>, n (%)</b>	77 (57)
<b>Bulky Disease<sup>d</sup>, n (%)</b>	44 (33)
<b>Extranodal Disease, n (%)</b>	101 (75)
<b>Number of Prior Systemic Anti-Lymphoma Therapies, n (%)</b>	
Median (range)	4 (2, 10)
1	0 (0)
2	29 (22)
3	34 (25)
$\geq$ 4	71 (53)
<b>Number of Subjects Who Received Prior Regimen Containing, n (%):</b>	
Anthracycline/mitoxantrone	133 (99)
Cyclophosphamide	133 (99)
Rituximab	134 (100)
Bortezomib	134 (100)

Baseline Disease Characteristics and Prior Anti - Lymphoma Treatment	Total Patients (N=134)
Refractory to Prior Bortezomib, n (%)	81 (60)
Refractory to Last Prior Therapy, n (%)	74 (55)
Prior Autologous Bone Marrow or Stem Cell Transplant, n (%)	39 (29)

<sup>a)</sup> ECOG = Eastern Cooperative Oncology Group

<sup>b)</sup> MIPI = MCL International Prognostic Index

<sup>c)</sup> High tumor burden is defined as at least one lesion that is  $\geq 5$  cm in diameter or 3 lesions that are  $\geq 3$  cm in diameter

<sup>d)</sup> Bulky disease is defined as at least one lesion that is  $\geq 7$ cm 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 16. The median time to response was 2.2 months (range 1.8 to 13 months).

**Table 16: 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 broken. 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.<sup>1</sup>

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 *Contraindications (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<sup>®</sup>” 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 [see *Warnings and Precautions (5.6)*].

**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 [see *Warnings and Precautions (5.7)*].

**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 [see *Warnings and Precautions (5.8)*].

**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 [see *Warnings and Precautions (5.9)*].

**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 [see *Warnings and Precautions (5.10)*].

**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

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Pat. [www.celgene.com/therapies](http://www.celgene.com/therapies)

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RevPlyPI.020/MG.020 02/15

**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 at least 4 weeks before starting REVLIMID
- while taking REVLIMID
- during any breaks (interruptions) in your treatment with REVLIMID
- for at least 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. Your healthcare provider should check your blood counts often especially during the first several months of treatment with REVLIMID, and then at least monthly. Tell your healthcare provider if you develop any bleeding or bruising, during treatment with REVLIMID.
- **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:

- if you have had a blood clot in the past
- if you have high blood pressure
- if you smoke
- if you have been told that you have a high level of fat in your blood (hyperlipidemia)
- 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:

- **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
- **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
- **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), in combination 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?”
- 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 open, break, or chew 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 Revlimid and melphalan, and a blood stem cell transplant have a higher risk of developing new cancers, including certain blood cancers (acute

myelogenous leukemia or AML, and myelodysplastic syndrome or MDS) 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 allergic reactions and serious skin reactions** can happen with REVLIMID and may cause death. Call your healthcare provider right away if you develop any of these signs or symptoms of a serious allergic reaction or serious skin reaction during treatment with REVLIMID:
  - swelling of your face, eyes, lips, tongue, throat
  - trouble swallowing
  - trouble breathing
  - skin rash, hives, or peeling of your skin
  - blisters
- **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.

**Common side effects of REVLIMID include:**

- diarrhea
- constipation
- itching
- rash
- tiredness
- swelling of the limbs and skin
- nausea
- fever
- cough

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](http://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 2015

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REVLIMID REMS<sup>™</sup> is a trademark of Celgene Corporation.

Pat.[www.celgene.com/therapies](http://www.celgene.com/therapies)

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**REVLIMID<sup>®</sup> (lenalidomide)**

**NDA 021880**

Celgene Corporation  
86 Morris Avenue  
Summit, NJ 07901

Contact Information:

**1-908-673-9000**  
**www.celgene.com**

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

**1. GOALS**

The goals of the REVLIMID risk evaluation and mitigation strategy are as follows:

1. To prevent the risk of embryo-fetal exposure to REVLIMID.
2. To inform prescribers, patients, and pharmacists on the serious risks and safe-use conditions for REVLIMID.

**2. REMS ELEMENTS**

**2.1. Elements to Assure Safe Use**

**2.1.1. Healthcare providers who prescribe REVLIMID are specially certified.**

Celgene will ensure that healthcare providers who prescribe REVLIMID are specially certified in the REVLIMID REMS<sup>™</sup> program.

To become certified, each prescriber must complete the Prescriber Enrollment Form and agree to do the following:

- a. Provide patient counseling on the benefits and risks of REVLIMID therapy, including risks described in the BOXED WARNINGS.
- b. Enroll each patient by completing and submitting to the Celgene Customer Care Center via mail (86 Morris Avenue, Summit, NJ 07901), email ([customercare@celgene.com](mailto:customercare@celgene.com)), fax (1-888-432-9325), or online ([www.celgeneriskmanagement.com](http://www.celgeneriskmanagement.com)), a signed Patient-Physician Agreement Form (PPAF) identifying the patient's risk category (see PPAFs for all six risk categories) for each new patient. In signing the PPAF, each prescriber acknowledges that they understand that REVLIMID is available only through the REVLIMID REMS<sup>™</sup> program, and that they must comply with program requirements.
- c. Provide contraception and emergency contraception counseling with each new prescription prior to and during REVLIMID treatment.

- d. Provide scheduled pregnancy testing for females of reproductive potential and verify negative pregnancy test results prior to writing a new prescription or subsequent prescriptions.
- e. Report any pregnancies in female patients or female partners of male patients prescribed REVLIMID immediately to Celgene Drug Safety (or Celgene Customer Care Center, 1-888-423-5436).
- f. Complete a prescriber survey (phone or online) for every patient (new and follow-up), obtain a unique prescription authorization number for each prescription written, and include this authorization number on the prescription. The authorization number can be obtained by contacting the Celgene Customer Care Center, using the automated IVR system, or via the [www.CelgeneRiskManagement.com](http://www.CelgeneRiskManagement.com) website.
  - o For females of reproductive potential, authorization numbers are valid only for 7 days from date of last pregnancy test and 30 days from the date it is issued for all other patients.
- g. Facilitate compliance with the mandatory REVLIMID REMS™ program patient survey by instructing patients to complete the mandatory surveys (phone or online) at program specified frequencies.
- h. Prescribe no more than a 4-week (28-day) supply, with no automatic refills or telephone prescriptions.
- i. Contact a REVLIMID REMS™ program pharmacy certified by the REVLIMID REMS™ program to fill the REVLIMID prescription.
- j. Return all unused REVLIMID brought in by patients to Celgene Customer Care.
- k. Re-enroll patients in the REVLIMID REMS™ program if REVLIMID is required and previous therapy with REVLIMID has been discontinued for 12 consecutive months.

Celgene will:

1. Ensure that the REVLIMID REMS™ program materials including prescriber enrollment are available on the [CelgeneRiskManagement.com](http://CelgeneRiskManagement.com) website or can be obtained by contacting Celgene Customer Care Center at 1-888-423-5436
2. Maintain a secure database of all REVLIMID REMS™ program certified prescribers.
3. Monitor to ensure that only REVLIMID REMS™ program certified prescribers are prescribing REVLIMID.
4. Monitor and ensure that patients have been assigned correctly to one of the following patient risk categories. Confirm risk category when completing the PPAFs during the patient enrollment process:
  - a. **Adult female of reproductive potential:** all females who are menstruating, amenorrheic from previous medical treatments, under 50 years, and/or perimenopausal.
  - b. **Female child of reproductive potential:** all females under 18 years who are menstruating.
  - c. **Adult female NOT of reproductive potential:** females who have had a natural menopause for at least 24 consecutive months, a hysterectomy, and/or bilateral oophorectomy.
  - d. **Female child NOT of reproductive potential:** all females under 18 years who are not menstruating.
  - e. **Adult males 18 years or older**
  - f. **Male child under 18 years**
5. Monitor certified prescriber compliance with the REVLIMID REMS™ program, including patient risk categorization and the appropriate corresponding counseling requirements, contraception requirements, pregnancy testing, and survey completion for all patients treated with REVLIMID.
6. Institute corrective action and prevent the certified prescriber from prescribing REVLIMID if the prescriber is found to be non-compliant with the REVLIMID REMS™ program.

7. Train REVLIMID REMS™ program certified prescribers in adverse experience reporting procedures, including the requirement to immediately report to Celgene any suspected embryo-fetal exposure to REVLIMID if a pregnancy occurs.
8. Ensure that once the prescriber submits the completed PPAF, the prescriber will receive a confirmation letter via fax or online to confirm the patient's enrollment and signify that the prescriber and patient surveys can be taken to receive an authorization number for the REVLIMID prescription (for all males, the PPAF is considered the initial survey). The authorization number is written on the REVLIMID prescription.
9. Ensure that, for subsequent prescriptions, the prescriber completes a telephone or online survey designed to look for signals of at-risk behavior (e.g., pending or outdated pregnancy test), report the patient's pregnancy test results, correct assignment of risk category, and confirm or re-enforce patient understanding of contraceptive requirements. The completion of the survey will allow the prescriber to obtain a new authorization number every time a prescription for REVLIMID is written.

The following materials are part of the REMS, and are appended:

- [Prescriber Enrollment Form](#)
- [Patient Prescription Form](#)
- [Patient Prescription Form \(Veterans Administration\)](#)
- [Prescriber Guide to REVLIMID REMS™ Program](#)
- [REVLIMID REMS™ At-A-Glance](#)
- [Welcome Letter](#)
- [Celgene Risk Management.com website](#)

**2.1.2. REVLIMID will only be dispensed by pharmacies that are specially certified.**

Celgene will ensure that REVLIMID is only dispensed from REVLIMID REMS™ program certified pharmacies. To become a certified pharmacy, the pharmacy must agree to do the following before filling a REVLIMID prescription:

- a. Only accept prescriptions with a prescription authorization number. Authorization numbers are valid for 7 days from date of last pregnancy test for females of reproductive potential and 30 days from the date it is issued for all other patients.
- b. Dispense no more than a 4-week (28-day) supply, and require a new prescription from the patient prior to dispensing additional REVLIMID.
- c. Dispense subsequent prescriptions only if there are 7 days or less remaining on an existing REVLIMID prescription.
- d. Obtain a REVLIMID REMS™ confirmation number from the Celgene Customer Care Center (phone or online) and write this confirmation number on the prescription. The REVLIMID REMS™ confirmation number may be obtained using the following procedure:
  1. Enter the pharmacy identification number (NABP or DEA);
  2. Enter the prescription authorization number written on the prescription;
  3. Enter the number of capsules and milligram (mg) strength being dispensed;
  4. Dispense or ship the prescribed REVLIMID within 24 hours of obtaining and recording the REVLIMID REMS™ confirmation number and confirmation date.

- e. Dispense REVLIMID only after a REVLIMID REMS™ program confirmation number is obtained. If no confirmation is obtained, then no REVLIMID is dispensed. Contact the patient's physician and Celgene for further instruction.
- f. Accept unused REVLIMID (previously dispensed) from a patient or patient caregiver and return to Celgene Corporation for proper disposal.
- g. For each patient receiving treatment, retain a record of each REVLIMID prescription dispensed and the corresponding completed REVLIMID REMS™ Education and Counseling Checklist.
- h. Complete the checklist that applies to the REVLIMID REMS™ program patient risk category written on the front of the Education and Counseling Checklist for Pharmacies.
- i. Provide counseling to patients and/or guardians of patients under 18 years of age receiving REVLIMID treatment.
  - a. Counsel all patients and guardians of patients under 18 years of age on the following:
    1. The benefits and risks of REVLIMID therapy.
    2. Not sharing REVLIMID medication
    3. Not donating blood while taking REVLIMID, during dose interruptions, and for 4 weeks after stopping REVLIMID.
    4. Not to break, chew, or open REVLIMID capsules.
    5. Instructions on REVLIMID dose and administration.
    6. To read the REVLIMID REMS™ program education materials and encourage compliance with the requirements.
  - b. In addition to above, counsel **Females of Reproductive Potential** on the following:
    1. The potential for embryo-fetal toxicity with exposure to REVLIMID.
    2. Using 2 forms of effective birth control at the same time or abstaining from heterosexual sexual intercourse.
    3. Continuing to use 2 forms of birth control if REVLIMID therapy is interrupted and for at least 4 weeks after therapy is discontinued.
    4. Obtaining a pregnancy test weekly during the first 4 weeks of REVLIMID use, then a repeat pregnancy test every 4 weeks in females with regular menstrual cycles, and every 2 weeks in females with irregular menstrual cycles.
    5. The need to stop taking REVLIMID and notify their REVLIMID prescriber immediately if they become pregnant or suspect they may be pregnant.
  - c. In addition to items listed for all patients above, counsel **Males** receiving REVLIMID treatment about the potential for embryo-fetal toxicity with exposure to REVLIMID and the importance of using barrier contraception by wearing a latex or synthetic condom when engaging in sexual intercourse with a female of reproductive potential even if the male receiving REVLIMID has had a successful vasectomy.
    1. The need to not donate sperm while taking REVLIMID, during dose interruptions, and for 4 weeks after stopping REVLIMID.
  - d. Counsel the **Parent or legal guardian of Female Child NOT of reproductive potential** who is receiving REVLIMID treatment about the need to inform their REVLIMID prescriber when the child begins menses.

Before a certified pharmacy dispenses REVLIMID, Celgene will train the appropriate pharmacy staff:

1. About the REVLIMID REMS™ program

2. About the procedures for reporting adverse experiences to Celgene, including the requirement to immediately report to Celgene any suspected embryo-fetal exposure to REVLIMID if a pregnancy occurs.

The following materials are part of the REMS, and are appended:

- [Pharmacy Guide to REVLIMID REMS™ Program](#)
- [Education and Counseling Checklist for Pharmacies](#)
- [Celgene REMS Programs Pharmacy Training: REVLIMID REMS™](#)
- [Pharmacy Certification Quiz \(the REVLIMID REMS™ Program\)](#)

**2.1.3. Celgene will ensure that REVLIMID® will only be dispensed to patients enrolled in the REVLIMID REMS™ program with evidence or other documentation of safe-use conditions.**

Celgene will ensure that all patients treated with REVLIMID are enrolled by a certified prescriber. The prescriber will enroll the patient by completing Patient-Physician Agreement Form and submitting the form via mail (86 Morris Avenue, Summit, NJ 07901), fax (1-888-432-9325), email ([customercare@celgene.com](mailto:customercare@celgene.com)) or online ([www.celgeneriskmanagement.com](http://www.celgeneriskmanagement.com)) for each patient who receives REVLIMID. Each patient and/or guardian of patients under 18 years of age consents to participate in the program by:

- a. acknowledging that he or she understands that:
  - i. severe birth defects or death to an unborn baby may occur if a female becomes pregnant while she is receiving REVLIMID;
  - ii. REVLIMID must not be shared with anyone, even someone with similar symptoms;
  - iii. REVLIMID must be kept out of the reach of children and should NEVER be shared with females who are able to have children;
  - iv. they cannot donate blood while receiving REVLIMID including during dose interruptions, and for 4 weeks after stopping REVLIMID;
  - v. they might be asked to participate in the REVLIMID Pregnancy Exposure Registry; and
  - vi. they may be contacted by Celgene about following the rules of the REMS.
- b. In addition, each patient and/or guardian of patients under 18 years of age consents to participate in the program by:
  - i. agreeing to return unused REVLIMID to Celgene or their REVLIMID prescriber, or to the pharmacy that dispensed the REVLIMID to them ;
  - ii. agreeing to participate in a monthly (telephone or online) survey while on REVLIMID (with the exception of Adult Females Not of Reproductive Potential who are required to take a survey once every six months); and
  - iii. reviewing the REVLIMID REMS™ program educational materials and asking their prescriber any questions that have not been answered.

In addition, **Females and guardians of female children** must attest to their understanding of their/their child's reproductive potential, as categorized by the prescribing physician.

**Females of Reproductive Potential and guardians of Female Children of Reproductive Potential** will attest that they/their child:

- a. is not currently pregnant, and will try to refrain from becoming pregnant while receiving REVLIMID therapy and for at least 4 weeks after completely stopping REVLIMID therapy;
- b. must not take REVLIMID if pregnant, breastfeeding a baby, or not using birth control as defined in the REMS;
- c. will, unless abstinent, use contraception as defined within the REMS: for at least 4 weeks before starting REVLIMID, while receiving REVLIMID, during dose interruptions, and for at least 4 weeks after stopping REVLIMID;
- d. will have pregnancy testing done as ordered by the certified prescriber within 10 to 14 days and 24 hours prior to starting REVLIMID, every week for at least the first 4 weeks of REVLIMID therapy, and then every 4 weeks if the Female of Reproductive Potential has regular menstrual cycles, or every 2 weeks if the Female of Reproductive Potential has irregular menstrual cycles, while receiving REVLIMID;
- e. will immediately stop taking REVLIMID and inform the certified prescriber if the patient becomes pregnant, misses a menstrual period, experiences unusual menstrual bleeding, stops using contraception, or thinks for any reason that she might be pregnant; if the prescriber is not available, the Female of Reproductive Potential or guardian of a Female Child of Reproductive Potential can call the Celgene Customer Care Center at 1-888-423-5436 or the Emergency Contraception Hotline at 1-888-668-2528 for information on emergency contraception.

**Males or Guardians of males** will attest that they/their child will:

- a. never have unprotected sexual contact with a female who can become pregnant;
- b. wear a latex or synthetic condom every time the male patient has sexual contact with a female who is or who can become pregnant; continue condom use with sexual contact while the male patient is receiving REVLIMID treatment, during dose interruptions, and for 4 weeks after the male patient stops taking REVLIMID, even if the patient has had a successful vasectomy; and
- c. inform their certified prescriber if the male patient has unprotected sexual contact with a female who can become pregnant, or if they think for any reason that the male patient's sexual partner might be pregnant; the male patient or guardian of an underage male patient can call the Celgene Customer Care Center at 1-888-423-5436 or the Emergency Contraception Hotline at 1-888-668-2528 for information on emergency contraception;
- d. not donate sperm while taking (including dose interruptions) and for 4 weeks after stopping REVLIMID

The following appended materials are part of the REMS:

- [Patient-Physician Agreement Form for Adult Male](#)
- [Patient-Physician Agreement Form for Male Child](#)
- [Patient-Physician Agreement Form for Adult Female Who Can Not Get Pregnant](#)
- [Patient-Physician Agreement Form for Adult Female Who Can Get Pregnant](#)
- [Patient-Physician Agreement Form for Female Child Who Can Not Get Pregnant](#)
- [Patient-Physician Agreement Form for Female Child Who Can Get Pregnant](#)
- [Patient Guide to REVLIMID REMS™ Program](#)
- [Emergency Contraception Brochure](#)
- [Patient Survey Reminder Card](#)

- REVLIMID Risk Evaluation and Mitigation Strategy (REMS)<sup>TM</sup> Program Education and Safety Kit
- REVLIMID REMS<sup>TM</sup> Patient Resource Pack Envelope

**2.1.4. Female patients or female partners of male patients receiving REVLIMID who report a pregnancy that occurred during REVLIMID therapy will be enrolled in the REVLIMID Pregnancy Exposure Registry.**

Upon receiving a report of pregnancy from the REVLIMID REMS<sup>TM</sup> program, Celgene Pregnancy Prevention Plan programs in the rest of the world, clinical trials, or directly from a prescriber, a pharmacy, or a patient, Celgene will enroll the female patient or female partner of the male patient taking REVLIMID into the REVLIMID Pregnancy Exposure Registry. The objectives of the registry are to monitor pregnancy outcomes in female patients of reproductive potential and male patients' female partners who are exposed to REVLIMID and to understand why the REVLIMID REMS<sup>TM</sup> program was unsuccessful.

## **2.2. Implementation System**

The implementation system will include the following:

- 1) Celgene will maintain a secure database of all certified entities, including enrolled patients and certified prescribers and pharmacies to monitor and evaluate implementation of the elements provided for in Sections 2.1.1, 2.1.2, and 2.1.3.
- 2) Celgene will monitor pharmacy certification compliance and address deviations by monitoring real time dispensing activity and conducting pharmacy audits.
  - a. The Celgene Customer Care Center will monitor the certified pharmacies in the manner described in the REMS supporting document to ensure only enrolled and authorized patients are receiving REVLIMID. If a certified pharmacy is found to be non-compliant with the REVLIMID REMS<sup>TM</sup> program, Celgene will institute corrective action and may de-activate pharmacies for which re-training has proven ineffective, removing them from the REVLIMID REMS<sup>TM</sup> program.
  - b. Celgene will perform regular audits of contract pharmacies participating in the REVLIMID REMS<sup>TM</sup> program. For pharmacies that have been in the program for more than two years, Celgene will perform a risk-based assessment to select which pharmacies will be audited. The REVLIMID REMS<sup>TM</sup> program compliance audits will be performed by internal auditors of Celgene and/or outside auditors contracted and trained by Celgene.
- 3) Celgene will monitor and ensure that the prescriptions are filled within the allowed timeframes.
- 4) Celgene Customer Care Center will address customer complaints received that are related to the REVLIMID REMS<sup>TM</sup> program and distribution and dispensing of REVLIMID.
- 5) Celgene will maintain a reporting and collection system for safety information that includes a process to monitor pregnancy testing results and pregnancy outcomes (should one occur) through the REVLIMID Pregnancy Exposure Registry and to understand why the REVLIMID REMS<sup>TM</sup> program was unsuccessful for the pregnancy case in question.
- 6) Based on monitoring and evaluation of these elements to assure safe use, Celgene will take reasonable steps to work to improve implementation of these elements as applicable.
- 7) Celgene will develop and follow written procedures related to the implementation of the REMS.

### **2.3. Timetable for Submission of Assessment Reports**

Celgene will submit REMS assessments at six months and then annually following the initial approval date of the REMS (August 3, 2010). To facilitate inclusion for as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Celgene will submit each assessment so it will be received by the FDA on or before the due date.