HIGHLIGHTS OF PRESCRIBING INFORMATION

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

REVLIMID (lenalidomide) capsules
Initial U.S. Approval: 2005

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

Fetal Risk

- **Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or death to a developing baby.**
- **Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception (5.2).**
- **REVLIMID is available only under a restricted distribution program called "RevAssist." (5.2, 17).**

Hematologic Toxicity

- **REVLIMID can cause significant neutropenia and thrombocytopenia (5.3).**

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

Deep Vein Thrombosis and Pulmonary Embolism

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

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

Boxed Warning	03/10
Indications and Usage (1.1, 1.2)	03/10
Dosage and Administration (2.1, 2.2)	03/10
Contraindications (4.1, 4.2)	03/10
Warnings and Precautions (5)	03/10
Patients with Renal Impairment (8.6)	03/10

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

REVLIMID is a thalidomide analogue indicated for the treatment of:

- Multiple myeloma (MM), in combination with dexamethasone, in patients who have received at least one prior therapy (1.1).
- Patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities (1.2).

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

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

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

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

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

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

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

- Females of childbearing potential: Must have 2 negative pregnancy tests before starting treatment with REVLIMID and must use two forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after treatment. Reproductive Risk and Special Prescribing Requirements: To avoid fetal exposure REVLIMID is only available under a special restricted distribution program called RevAssist (Boxed Warnings, 4.1, 5.1, 17).
- Hematologic Toxicity: This drug is associated with significant neutropenia and thrombocytopenia. Patients may require dose interruption and/or dose reduction (5.3, 6.1).
- Deep vein thrombosis and pulmonary embolism: Physicians and patients should be observant for signs and symptoms of thromboembolism (5.4, 6.1).
- Allergic Reactions: include hypersensitivity, angioedema, Stevens-Johnson syndrome, and toxic epidermal necrolysis. In some cases these allergic reactions may be fatal. Discontinue REVLIMID if any such reactions are suspected (5.5). REVLIMID should not be resumed following discontinuation for these reactions.
- Tumor lysis syndrome (TLS): Fatal instances of TLS have been reported during treatment with lenalidomide. Monitor patients at risk of TLS (i.e., those with high tumor burden) and take appropriate precautions (5.6).
- Tumor flare reaction: Serious tumor flare reactions have occurred during investigational use of REVLIMID for chronic lymphocytic leukemia and lymphoma (5.7).

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

- MM: Most common adverse reactions (≥20%) include fatigue, neutropenia, constipation, diarrhea, muscle cramp, anemia, pyrexia, peripheral edema, nausea , back pain, upper respiratory tract infection, dyspnea, dizziness, thrombocytopenia, tremor and rash (6.1)
- MDS: Most common adverse reactions (>15%) include thrombocytopenia, neutropenia, diarrhea, pruritus, rash , fatigue, constipation, nausea, , nasopharyngitis, arthralgia, pyrexia, back pain, peripheral edema, cough, dizziness, headache, muscle cramp, dyspnea, pharyngitis, and epistaxis (6.2).

To report SUSPECTED ADVERSE REACTIONS; contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-332-1088 or *www.fda.gov/medwatch*.

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

- Digoxin: Periodic monitoring of digoxin plasma levels is recommended due to increased C_{max} with concomitant REVLIMID therapy (7.1).
- Patients taking concomitant therapies such as erythropoietin stimulating agents or estrogen containing therapies, may have an increased risk of venous thromboembolic events (VTE). (7.3)

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

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: ____

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

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

Do not use REVLIMID during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or death to a developing baby. In women of childbearing potential, obtain 2 negative pregnancy tests before starting REVLIMID® treatment. Women of childbearing potential must use 2 forms of contraception or

continuously abstain from heterosexual sex during and for 4 weeks after REVLIMID treatment [*see Warnings and Precautions (5.1), and Medication Guide (17)*]. To avoid fetal exposure to lenalidomide, REVLIMID is only available under a restricted distribution program called "RevAssist®" (5.2).

Information about the RevAssist program is available at www.REVLIMID.com or by calling the manufacturer's toll-free number 1-888-423-5436.

Hematologic Toxicity (Neutropenia and Thrombocytopenia)

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

Deep Vein Thrombosis and Pulmonary Embolism

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Multiple Myeloma

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

1.2 Myelodysplastic Syndromes

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

2 DOSAGE AND ADMINISTRATION

2.1 Multiple Myeloma

The recommended starting dose of REVLIMID is 25 mg once daily orally with water on Days 1-21 of repeated 28-day cycles. Patients should not break, chew or open the capsules. The recommended dose of dexamethasone is 40 mg once daily on Days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily orally on Days 1-4 every 28 days. Treatment is continued or modified based upon clinical and laboratory findings.

Dose Adjustments for Hematologic Toxicities During Multiple Myeloma Treatment

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

Platelet counts

Thrombocytopenia in MM

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

Absolute Neutrophil counts (ANC)

Neutropenia in MM

When Neutrophils	Recommended Course
Fall to <1000/mcL	Interrupt REVLIMID treatment, add G-CSF, follow CBC weekly
Return to ≥1,000/mcL and neutropenia is the only toxicity	Resume REVLIMID at 25 mg daily
Return to ≥1,000/mcL and if other toxicity	Resume REVLIMID at 15 mg daily

For each subsequent drop <1,000/mcL Return to ≥1,000/mcL	Interrupt REVLIMID treatment Resume REVLIMID at 5 mg less than the previous dose. Do not dose below 5 mg daily

Other Grade 3 / 4 Toxicities in MM

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

Starting Dose Adjustment for Renal Impairment in MM

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

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

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

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

2.2 Myelodysplastic Syndromes

The recommended starting dose of REVLIMID is 10 mg daily with water. Patients should not break, chew or open the capsules. Treatment is continued or modified based upon clinical and laboratory findings.

Dose Adjustments for Hematologic Toxicities During MDS Treatment

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

Platelet counts

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

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

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

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

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

If thrombocytopenia develops during treatment at 5 mg daily in MDS

When Platelets	Recommended Course
<30,000/mcL or <50,000/mcL with platelet transfusions	Interrupt REVLIMID treatment

Return to ≥30,000/mcL (without hemostatic failure)	Resume REVLIMID at 5 mg every other day

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

Absolute Neutrophil counts (ANC)

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

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

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

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

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

If neutropenia develops during treatment at 5 mg daily in MDS

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

Starting Dose Adjustment for Renal Impairment in MDS:

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

Table 2: Starting Dose Adjustment for Renal Impairment in Myelodysplastic Syndromes (Days 1 – 28 of each 28 day cycle)

Category	**Renal Function (Cockcroft-Gault)**	**Dose**
Moderate Renal Impairment	CLcr 30-60 mL/min	5 mg Every 24 hours
Severe Renal Impairment	CLcr < 30 mL/min (not requiring dialysis)	5 mg Every 48 hours
End Stage Renal Disease	CLcr < 30 mL/min (requiring dialysis)	5 mg 3 times a week following each dialysis

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

3 DOSAGE FORMS AND STRENGTHS

REVLIMID 5 mg, 10 mg, 15 mg and 25 mg capsules will be supplied through the RevAssist program

REVLIMID is available in the following capsule strengths:

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
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 may cause fetal harm when administered to a pregnant woman. 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 pregnant women and women capable of becoming pregnant *[see Boxed Warning]*. Females of childbearing potential may be treated with lenalidomide provided adequate precautions are taken to avoid pregnancy. Females must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control, including at least one highly effective method (e.g., hormonal contraception, tubal ligation, IUD or partner's vasectomy) and one additional effective method (e.g., latex condom, diaphragm, or cervical cap), beginning 4 weeks prior to initiating treatment with REVLIMID, during therapy, during therapy delay, and continuing for 4 weeks following discontinuation of REVLIMID therapy. If hormonal or IUD contraception is medically contraindicated, two other effective or highly effective methods may be used.

Females of childbearing potential being treated with REVLIMID must have pregnancy testing (sensitivity of at least 50 mIU/mL). The first test should be performed within 10-14 days and the second test within 24 hours prior to beginning 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. Pregnancy testing and counseling must be performed if a patient misses her period or if there is any abnormality in menstrual bleeding. If pregnancy occurs, REVLIMID must be immediately discontinued. Under these conditions, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

4.2. Allergic Reactions

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

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Risk

REVLIMID is a thalidomide analogue. Thalidomide is a known human teratogen that causes life-threatening human birth defects. An embryofetal development study in non-human primates 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. If REVLIMID is used during pregnancy, it may cause birth defects or death to a developing baby. Females of childbearing potential must be advised to avoid pregnancy while on REVLIMID. Two effective contraceptive methods should be used during therapy, during therapy interruptions and for at least 4 weeks after completing therapy.

There are no adequate and well-controlled studies in pregnant females.

5.2 Reproductive Risk and Special Prescribing Requirements (RevAssist Program)

Because of this potential toxicity and to avoid fetal exposure, REVLIMID is only available under a special restricted distribution program called "RevAssist". Prescribers and pharmacists registered with the program can prescribe and dispense the product to patients who are registered and meet all the conditions of the RevAssist program.

Please see the following information for prescribers, female patients, and male patients about this restricted distribution program.

RevAssist Program Description

Prescribers

REVLIMID can be prescribed only by licensed prescribers who are registered in the RevAssist program and understand the potential risk of teratogenicity if lenalidomide is used during pregnancy.

Effective contraception must be used by female patients of childbearing potential for at least 4 weeks before beginning REVLIMID therapy, during therapy, during dose interruptions and 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 or because the patient has been postmenopausal naturally for at least 24 consecutive months. Females of childbearing potential should be referred to a qualified provider of contraceptive methods, if needed. Sexually mature females who have not undergone a hysterectomy, have not had a bilateral oophorectomy or who have not been postmenopausal naturally for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months) are considered to be females of childbearing potential. Two reliable forms of contraception must be used simultaneously unless continuous abstinence from heterosexual sexual contact is the chosen method.

Females of childbearing potential must have 2 negative pregnancy tests (sensitivity of at least 50 mIU/mL). The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing REVLIMID. A prescription for REVLIMID for a female of childbearing potential must not be issued by the prescriber until negative pregnancy tests have been verified by the prescriber.

Male Patients: It is not known whether lenalidomide is present in the semen of patients receiving the drug. Therefore, males receiving REVLIMID must always use a latex condom during any sexual contact with females of childbearing potential even if they have undergone a successful vasectomy.

Once treatment has started and during dose interruptions, pregnancy testing for females of childbearing 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 pregnancy test or in her menstrual bleeding. REVLIMID treatment must be discontinued during this evaluation.

Pregnancy test results should be verified by the prescriber and the pharmacist prior to dispensing any prescription.

If pregnancy does occur during treatment, REVLIMID must be discontinued immediately.

Any suspected fetal exposure to REVLIMID must be reported to the FDA via the MedWatch number at 1-800-332-1088 and also to Celgene Corporation at 1-888-423-5436. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Female Patients

REVLIMID may be used in females of childbearing potential only when the PATIENT MEETS ALL OF THE FOLLOWING CONDITIONS (i.e., she is unable to become pregnant while on REVLIMID therapy):

- she is capable of complying with the mandatory contraceptive measures, pregnancy testing, patient registration, and patient survey as described in the RevAssist program.
- she has received and understands both oral and written warnings of the potential risks of taking REVLIMID during pregnancy and of exposing a fetus to the drug.
- she has received both oral and written warnings of the risk of possible contraception failure and of the need to use two reliable forms of contraception simultaneously (one highly effective form of contraception – tubal ligation, IUD, hormonal (birth control pills, injections, patch or implants) or partner's vasectomy and one additional effective contraceptive method - latex condom, diaphragm or cervical cap, unless continuous abstinence from heterosexual sexual contact is the chosen method. Sexually mature females who have not undergone a hysterectomy or who have not been postmenopausal for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months), or had a bilateral oophorectomy are considered to be females of childbearing potential.
- she acknowledges, in writing, her understanding of these warnings and of the need for using two reliable methods of contraception for 4 weeks prior to beginning REVLIMID therapy, during therapy, during dose interruptions and for 4 weeks after discontinuation of therapy.
- she has had two negative pregnancy tests with a sensitivity of at least 50 mIU/mL, within 10-14 days and 24 hours prior to beginning therapy.
- if the patient is between 12 and 18 years of age, her parent or legal guardian must have read the educational materials and agreed to ensure compliance with the above.

Male Patients

REVLIMID may be used in sexually active males when the PATIENT MEETS ALL OF THE FOLLOWING CONDITIONS:

- he is capable of complying with the mandatory contraceptive measures that are appropriate for men, patient registration, and patient survey as described in the RevAssist program.
- he has received and understands both oral and written warnings of the potential risks of taking REVLIMID and exposing a fetus to the drug.
- he has received both oral and written warnings of the risk of possible contraception failure and that it is unknown whether lenalidomide is present in semen. He has been instructed that he must always use a latex condom during any sexual contact with females of childbearing potential, even if he has undergone a successful vasectomy. Females of childbearing potential are considered to be sexually mature females who have not undergone a hysterectomy, have not had a bilateral oophorectomy or who have not been postmenopausal for at least 24 consecutive months (i.e., who have had menses at any time in the preceding 24 consecutive months).
- he acknowledges, in writing, his understanding of these warnings and of the need to use a latex condom during any sexual contact with females of childbearing potential, even if he has undergone a successful vasectomy.
- if the patient is between 12 and 18 years of age, his parent or legal guardian must have read the educational materials and agreed to ensure compliance with the above.

5.3 Hematologic Toxicity

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

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

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

5.4 Deep Vein Thrombosis and Pulmonary Embolism

Venous thromboembolic events (predominantly deep venous thrombosis and pulmonary embolism) have occurred in patients with multiple myeloma treated with lenalidomide combination therapy *[see Boxed Warning]* and patients with MDS treated with lenalidomide monotherapy. A significantly increased risk of DVT and PE was observed in patients with multiple myeloma who were treated with REVLIMID and dexamethasone therapy in a clinical trial *[see Boxed Warning]*. It is not known whether prophylactic

anticoagulation or antiplatelet therapy prescribed in conjunction with REVLIMID may lessen the potential for venous thromboembolic events. The decision to take prophylactic measures should be done carefully after an assessment of an individual patient's underlying risk factors.

5.5 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.

5.6 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.

5.7 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. Treatment of CLL or lymphoma with lenalidomide outside of a well-monitored clinical trial is discouraged.

6. ADVERSE REACTIONS

The following adverse reactions are described in detail in other labeling sections:

- Neutropenia and thrombocytopenia *[see Boxed Warnings, Warnings and Precautions (5.3)]*
- Deep vein thrombosis, and pulmonary embolism *[see Boxed Warnings, Warnings and Precautions (5.4)]*
- Allergic Reactions *[see Warnings and Precautions (5.5)]*
- Tumor lysis syndrome *[see Warnings and Precautions (5.6)*
- Tumor flare reactions *[see Warnings and Precautions (5.7)]*

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

6.1 Clinical Trials Experience in Multiple Myeloma

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

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

Tables 3, 4, and 5 summarize the adverse reactions reported for REVLIMID/dexamethasone and placebo/dexamethasone groups.

Table 3: 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	Lenalidomide/Dex* (n=353) n (%)	Placebo/Dex * (n=350) n (%)
Blood and lymphatic system disorders		
Neutropenia [%]	149 (42.2)	22 (6.3)
Anemia [@]	111 (31.4)	83 (23.7)
Thrombocytopenia [@]	76 (21.5)	37 (10.6)
Leukopenia	28 (7.9)	4 (1.1)
Lymphopenia	19 (5.4)	5 (1.4)
General disorders and administration site conditions		
Fatigue	155 (43.9)	146 (41.7)
Pyrexia	97 (27.5)	82 (23.4)
Peripheral edema	93 (26.3)	74 (21.1)
Chest Pain	29 (8.2)	20 (5.7)
Lethargy	24 (6.8)	8 (2.3)
Gastrointestinal disorders		
Constipation	143 (40.5)	74 (21.1)
Diarrhea[@]	136 (38.5)	96 (27.4)
Nausea [@]	92 (26.1)	75 (21.4)
Vomiting [@]	43 (12.2)	33 (9.4)
Abdominal Pain [@]	35 (9.9)	22 (6.3)
Dry Mouth	25 (7.1)	13 (3.7)
Musculoskeletal and connective tissue disorders		
Muscle cramp	118 (33.4)	74 (21.1)
Back pain	91 (25.8)	65 (18.6)
Bone Pain	48 (13.6)	39 (11.1)
Pain in Limb	42 (11.9)	32 (9.1)
Nervous system disorders		
Dizziness	82 (23.2)	59 (16.9)
Tremor	75 (21.2)	26 (7.4)
Dysgeusia	54 (15.3)	34 (9.7)
Hypoaesthesia	36 (10.2)	25 (7.1)
Neuropathy [a]	23 (6.5)	13 (3.7)
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	83 (23.5)	60 (17.1)
Nasopharyngitis	62 (17.6)	31 (8.9)
Pharyngitis	48 (13.6)	33 (9.4)
Bronchitis	40 (11.3)	30 (8.6)
Infections[b] and infestations		
Upper respiratory tract infection	87 (24.6)	55 (15.7)
Pneumonia [@]	48 (13.6)	29 (8.3)
Urinary Tract Infection	30 (8.5)	19 (5.4)
Sinusitis	26 (7.4)	16 (4.6)
Skin and subcutaneous system disorders		
Rash [c]	75 (21.2)	33 (9.4)
Sweating Increased	35 (9.9)	25 (7.1)
Dry Skin	33 (9.3)	14 (4.0)
Pruritus	27 (7.6)	18 (5.1)
Metabolism and nutrition disorders		
Anorexia	55 (15.6)	34 (9.7)

System Organ Class/ Preferred Term	Lenalidomide/Dex* (n=353) n (%)	Placebo/Dex * (n=350) n (%)
Hypokalemia	48 (13.6)	21 (6.0)
Hypocalcemia	31 (8.8)	10 (2.9)
Appetite Decreased	24 (6.8)	14 (4.0)
Dehydration	23 (6.5)	15 (4.3)
Hypomagnesaemia	24 (6.8)	10 (2.9)
Investigations		
Weight Decreased	69 (19.5)	52 (14.9)
Eye disorders		
Blurred vision	61 (17.3)	40 (11.4)
Vascular disorders		
Deep vein thrombosis [%]	33 (9.3)	15 (4.3)
Hypertension	28 (7.9)	20 (5.7)
Hypotension	25 (7.1)	15 (4.3)

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

System Organ Class/ Preferred Term	Lenalidomide/Dex[#] (n=353) n (%)	Placebo/Dex[#] (n=350) n (%)
Cardiac Failure Congestive [@]	5 (1.4)	1 (0.3)
Nervous System disorders		
Syncope	10 (2.8)	3 (0.9)
Dizziness	7 (2.0)	3 (0.9)
Eye Disorders		
Cataract	6 (1.7)	1 (0.3)
Cataract Unilateral	5 (1.4)	0 (0.0)
Psychiatric Disorder		
Depression	10 (2.8)	6 (1.7)

Table 5: Serious Adverse Events 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	Lenalidomide/Dex[&] (n=353) n (%)	Placebo/Dex[&] (n=350) n (%)
Blood and lymphatic system disorders		
Febrile Neutropenia[%]	6 (1.7)	0 (0.0)
Vascular disorders		
Deep vein thrombosis[%]	26 (7.4)	11 (3.1)
Infections[b] and infestations		
Pneumonia [@]	33 (9.3)	21 (6.0)
Respiratory, thoracic, and mediastinal disorders		
Pulmonary embolism[@]	13 (3.7)	3 (0.9)
Cardiac disorders		
Atrial fibrillation [@]	11 (3.1)	2 (0.6)
Cardiac Failure Congestive [@]	5 (1.4)	0 (0.0)
Nervous system disorders		
Cerebrovascular accident [@]	7 (2.0)	3 (0.9)
Gastrointestinal disorders		
Diarrhea [@]	6 (1.7)	2 (0.6)
Musculoskeletal and connective tissue disorders		
Bone Pain	4 (1.1)	0 (0.0)

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

Venous Thromboembolism

Deep Vein Thrombosis and Pulmonary Embolism ***[see Warnings and Precautions (5.3)]***

Deep vein thrombosis (DVT) was reported as a serious adverse drug reaction (7.4%) or Grade 3/4 (8.2%) at a higher rate in the REVLIMID/dexamethasone group compared to 3.1 % and 3.4% in the placebo/dexamethasone group, respectively. Discontinuations due to DVT adverse reactions were reported at comparable rates between groups.

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

Other Adverse Events

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

Blood and lymphatic system disorders: pancytopenia, autoimmune hemolytic anemia

Cardiac disorders: bradycardia, myocardial infarction, angina pectoris

Endocrine disorders: hirsutism

Eye disorders: blindness, ocular hypertension

Gastrointestinal disorders: gastrointestinal hemorrhage, glossodynia

General disorders and administration site conditions: malaise

Investigations: liver function tests abnormal, alanine aminotransferase increased,

Nervous system disorders: cerebral ischemia

Psychiatric disorders: mood swings, hallucination loss of libido

Reproductive system and breast disorders: erectile dysfunction,

Respiratory, thoracic and mediastinal disorders: cough, hoarseness

Skin and subcutaneous tissue disorders: exanthem, skin hyperpigmentation

6.2 Clinical Trials Experience in Myelodysplastic Syndromes

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

Thrombocytopenia (61.5%; 91/148) and neutropenia (58.8%; 87/148) were the most frequently reported adverse events. The next most common adverse events observed were diarrhea (48.6%; 72/148), pruritus (41.9%; 62/148), rash (35.8%; 53/148) and fatigue (31.1%; 46/148). Table 6 summarizes the adverse events that were reported in ≥ 5% of the REVLIMID treated patients in the del 5q MDS clinical study. Table 7 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 6: Summary of Adverse Events Reported in ≥5% of the REVLIMID Treated Patients in del 5q MDS Clinical Study

System organ class/Preferred term [a]	10 mg Overall (N=148)	
Patients with at least one adverse event	148	(100.0)
Blood and Lymphatic System Disorders		
Thrombocytopenia	91	(61.5)
Neutropenia	87	(58.8)
Anemia	17	(11.5)
Leukopenia	12	(8.1)
Febrile Neutropenia	8	(5.4)
Skin and Subcutaneous Tissue Disorders		
Pruritus	62	(41.9)
Rash	53	(35.8)
Dry Skin	21	(14.2)
Contusion	12	(8.1)
Night Sweats	12	(8.1)
Sweating Increased	10	(6.8)
Ecchymosis	8	(5.4)
Erythema	8	(5.4)
Gastrointestinal Disorders		
Diarrhea	72	(48.6)
Constipation	35	(23.6)
Nausea	35	(23.6)
Abdominal Pain	18	(12.2)
Vomiting	15	(10.1)
Abdominal Pain Upper	12	(8.1)

Dry Mouth	10	(6.8)
Loose Stools	9	(6.1)
Respiratory, Thoracic and Mediastinal Disorders		
Nasopharyngitis	34	(23.0)
Cough	29	(19.6)
Dyspnea	25	(16.9)
Pharyngitis	23	(15.5)
Epistaxis	22	(14.9)
Dyspnea Exertional	10	(6.8)
Rhinitis	10	(6.8)
Bronchitis	9	(6.1)
General Disorders and Administration Site Conditions		
Fatigue	46	(31.1)
Pyrexia	31	(20.9)
Edema Peripheral	30	(20.3)
Asthenia	22	(14.9)
Edema	15	(10.1)
Pain	10	(6.8)
Rigors	9	(6.1)
Chest Pain	8	(5.4)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	32	(21.6)
Back Pain	31	(20.9)
Muscle Cramp	27	(18.2)
Pain in Limb	16	(10.8)
Myalgia	13	(8.8)
Peripheral Swelling	12	(8.1)
Nervous System Disorders		
Dizziness	29	(19.6)
Headache	29	(19.6)
Hypoesthesia	10	(6.8)
Dysgeusia	9	(6.1)
Peripheral Neuropathy	8	(5.4)
Infections and Infestations		
Upper Respiratory Tract Infection	22	(14.9)
Pneumonia	17	(11.5)
Urinary Tract Infection	16	(10.8)
Sinusitis	12	(8.1)
Cellulitis	8	(5.4)
Metabolism and Nutrition Disorders		
Hypokalemia	16	(10.8)
Anorexia	15	(10.1)
Hypomagnesemia	9	(6.1)
Investigations		
Alanine Aminotransferase Increased	12	(8.1)
Psychiatric Disorders		
Insomnia	15	(10.1)
Depression	8	(5.4)
Renal and Urinary Disorders		
Dysuria	10	(6.8)
Vascular Disorders		
Hypertension	9	(6.1)
Endocrine Disorders		
Acquired Hypothyroidism	10	(6.8)
Cardiac Disorders		
Palpitations	8	(5.4)

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

483
484
485

Table 7: Most Frequently Observed Grade 3 and 4 Adverse Events [1] Regardless of Relationship to Study Drug Treatment

Preferred term [2]	10 mg (N=148)	
Patients with at least one Grade 3/4 AE	131	(88.5)
Neutropenia	79	(53.4)
Thrombocytopenia	74	(50.0)
Pneumonia	11	(7.4)
Rash	10	(6.8)
Anemia	9	(6.1)
Leukopenia	8	(5.4)

Fatigue	7	(4.7)
Dyspnea	7	(4.7)
Back Pain	7	(4.7)
Febrile Neutropenia	6	(4.1)
Nausea	6	(4.1)
Diarrhea	5	(3.4)
Pyrexia	5	(3.4)
Sepsis	4	(2.7)
Dizziness	4	(2.7)
Granulocytopenia	3	(2.0)
Chest Pain	3	(2.0)
Pulmonary Embolism	3	(2.0)
Respiratory Distress	3	(2.0)
Pruritus	3	(2.0)
Pancytopenia	3	(2.0)
Muscle Cramp	3	(2.0)
Respiratory Tract Infection	2	(1.4)
Upper Respiratory Tract Infection	2	(1.4)
Asthenia	2	(1.4)
Multi-organ Failure	2	(1.4)
Epistaxis	2	(1.4)
Hypoxia	2	(1.4)
Pleural Effusion	2	(1.4)
Pneumonitis	2	(1.4)
Pulmonary Hypertension	2	(1.4)
Vomiting	2	(1.4)
Sweating Increased	2	(1.4)
Arthralgia	2	(1.4)
Pain in Limb	2	(1.4)
Headache	2	(1.4)
Syncope	2	(1.4)

[1] Adverse events with frequency ≥1% in the 10 mg Overall group. Grade 3 and 4 are based on National Cancer Institute Common Toxicity Criteria version 2.

[2] Preferred Terms are coded using the MedDRA dictionary. A patient with multiple occurrences of an AE is counted only once in the Preferred Term category.

In other clinical studies of REVLIMID in MDS patients, the following serious adverse events (regardless of relationship to study drug treatment) not described in Table 6 or 7 were reported:

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

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

Ear and labyrinth disorders: vertigo

Endocrine disorders: Basedow's disease

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

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

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

Immune system disorders: hypersensitivity

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

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

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

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

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

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

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

Psychiatric disorders: confusional state

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

Reproductive system and breast disorders: pelvic pain

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

Skin and subcutaneous tissue disorders: acute febrile neutrophilic dermatosis

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

6.3 Postmarketing Experience

The following adverse drug reactions have been identified from the worldwide post-marketing experience with REVLIMID. Because these reactions are reported voluntarily, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: Allergic reactions (angioedema, Stevens-Johnson syndrome, and toxic epidermal necrolysis), tumor lysis syndrome (TLS) and tumor flare reaction (TFR) *[see Warnings and Precautions Section (5.5 to 5.7)]*.

7 DRUG INTERACTIONS

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

7.1 Digoxin

When digoxin was co-administered with lenalidomide, the digoxin AUC was not significantly different; however, the digoxin C_{max} was 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 lenalidomide.

7.2 Warfarin

Co-administration of multiple doses of 10 mg of lenalidomide had no effect on the single dose pharmacokinetics of R- and S-warfarin. Co-administration of single 25-mg dose warfarin had no effect on the pharmacokinetics of total lenalidomide. Expected changes in laboratory assessments of PT and INR were observed after warfarin administration, but these changes were not affected by concomitant lenalidomide administration.

7.3 Concomitant Therapies That May Increase the Risk of Thrombosis

Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone (see section 5.4).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

REVLIMID can cause fetal harm when administered to a pregnant woman. REVLIMID is contraindicated in women who are or may become pregnant. There are no adequate and well-controlled studies in pregnant women. However, in an animal study, 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 1-800-332-1088 and also to Celgene Corporation at 1-888-423-5436.

In an embryofetal developmental toxicity study in monkeys, teratogenicity, including thalidomide-like limb defects, occurred in offspring when pregnant monkeys received oral lenalidomide during organogenesis at doses approximately 0.17 times the maximum recommended human dose (MRHD) of 25 mg, based on body surface area. Similar studies in pregnant rabbits and rats at 20 times and 200 times the MRHD respectively, produced embryolethality in rabbits and no adverse reproductive effects in rats. In another study, pregnant rats received lenalidomide from organogenesis through lactation, some delay in sexual maturation occurred in male offspring. As with thalidomide, the rat model may not adequately address the full spectrum of potential human embryofetal developmental effects for lenalidomide.

Females of childbearing potential must use effective means of contraception for 28 days before therapy, during lenalidomide therapy and dose interruptions, and for 28 days following discontinuation of lenalidomide therapy, or continually abstain from reproductive heterosexual sexual intercourse. Because of the increased risk of VTE in patients with multiple myeloma taking lenalidomide and dexamethasone, and to a lesser extent patients with MDS taking lenalidomide monotherapy, and because there is an increased risk of VTE in patients taking combined oral contraceptive pills, physicians should discuss the risk/benefit of contraceptive methods with their patients.

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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

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

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

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

8.6 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 or severe renal impairment (CLcr < 60 mL/min) and in patients on dialysis *[see Dosage and Administration (2.1, 2.2)]*.

8.7 Hepatic Impairment

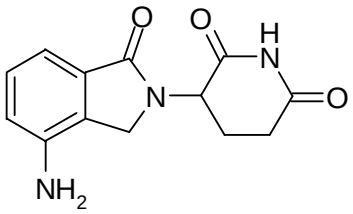
No study has been conducted in patients with hepatic impairment.

10. OVERDOSAGE

No cases of overdose have been reported during the clinical studies.

11. DESCRIPTION

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



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

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

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

REVLIMID is available in 5 mg, 10 mg, 15 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 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.

12 CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory, antiangiogenic, and antineoplastic properties. Experiments have demonstrated that lenalidomide inhibits the growth of cells derived from patients with multiple myeloma 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. Lenalidomide inhibits the secretion of pro-inflammatory cytokines

such as tumor necrosis factor alpha (TNF-α), from peripheral blood mononuclear cells. Lenalidomide also inhibited the expression of cycoloxygenase-2 (COX-2) but not COX-1 *in vitro*.

12.3 Pharmacokinetics

Absorption

Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration (C_{max}) by 36%. The pharmacokinetic disposition of lenalidomide is linear. C_{max} and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Pharmacokinetic sampling in myelodysplastic syndromes patients was not performed. In multiple myeloma patients maximum plasma concentrations occurred between 0.5 and 4.0 hours post-dose both on Days 1 and 28. AUC and C_{max} values increase proportionally with dose following single and multiple doses. Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

Distribution

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

Metabolism and Excretion

The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.

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

In multiple myeloma 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 (2.1, 2.2)]*.

Patients with Hepatic Disease: The pharmacokinetics of lenalidomide in patients with hepatic impairment have not been studied.

Age: The effects of age on the pharmacokinetics of lenalidomide have not been studied.

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

Gender: The effects of gender on the pharmacokinetics of lenalidomide have not been studied.

Race: Pharmacokinetic differences due to race have not been studied.

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity: Carcinogenicity studies with lenalidomide have not been conducted.

Mutagenesis: Lenalidomide did not induce mutation in the Ames test, chromosome aberrations in cultured human peripheral blood lymphocytes, or mutation 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.

Fertility: 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.

13.3. Reproductive and Developmental Toxicity

Lenalidomide had an embryocidal effect in rabbits at a dose of 50 mg/kg (approximately 120 times the human dose of 10 mg based on body surface area)

In an embryofetal developmental toxicity study in monkeys, teratogenicity, including thalidomide-like limb defects, occurred in offspring when pregnant monkeys received oral lenalidomide during organogenesis at doses approximately 0.17times the maximum recommended human dose (MRHD) of 25 mg, based on body surface area.

A pre- and post-natal development study in rats revealed 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.

14. CLINICAL STUDIES

14.1. Multiple Myeloma

Two randomized studies (Studies 1 and 2) were conducted to evaluate the efficacy and safety of REVLIMID. These multicenter, multinational, double-blind, placebo-controlled studies compared REVLIMID plus oral pulse high-dose dexamethasone therapy to dexamethasone therapy alone in patients with multiple myeloma who had received at least one prior treatment. These studies enrolled patients with absolute neutrophil counts (ANC) $\geq 1000/mm^3$, platelet counts $\geq 75{,}000/mm^3$, serum creatinine ≤ 2.5 mg/dL, serum SGOT/AST or SGPT/ALT ≤ 3.0 x upper limit of normal (ULN), and serum direct bilirubin ≤ 2.0 mg/dL.

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

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

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

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

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

	Study 1		Study 2	
	REVLIMID/Dex N=177	**Placebo/Dex N=176**	**REVLIMID/Dex N=176**	**Placebo/Dex N=175**
Patient Characteristics				
Age (years) Median Min, Max	 64 36, 86	 62 37, 85	 63 33, 84	 64 40, 82
Sex Male Female	 106 (60%) 71 (40%)	 104 (59%) 72 (41%)	 104 (59%) 72 (41%)	 103 (59%) 72 (41%)
Race/Ethnicity White Other	 141(80%) 36 (20%)	 148 (84%) 28 (16%)	 172 (98%) 4 (2%)	 175(100%) 0 (0%)
ECOG Performance Status 0-1	 157 (89%)	 168 (95%)	 150 (85%)	 144 (82%)
Disease Characteristics				
Multiple Myeloma Stage (Durie-Salmon) I II III	 3% 32% 64%	 3% 31% 66%	 6% 28% 65%	 5% 33% 63%
B2-microglobulin (mg/L) ≤ 2.5 mg/L > 2.5 mg/L	 52 (29%) 125 (71%)	 51 (29%) 125 (71%)	 51 (29%) 125 (71%)	 48 (27%) 127 (73%)
Number of Prior Therapies				
1 ≥ 2	38% 62%	38% 62%	32% 68%	33% 67%
Types of Prior Therapies				
Stem Cell Transplantation	62%	61%	55%	54%
Thalidomide	42%	46%	30%	38%
Dexamethasone	81%	71%	66%	69%
Bortezomib	11%	11%	5%	4%
Melphalan	33%	31%	56%	52%
Doxorubicin	55%	51%	56%	57%

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

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

Table 9. TTP Results in Study 1 and Study 2

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

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

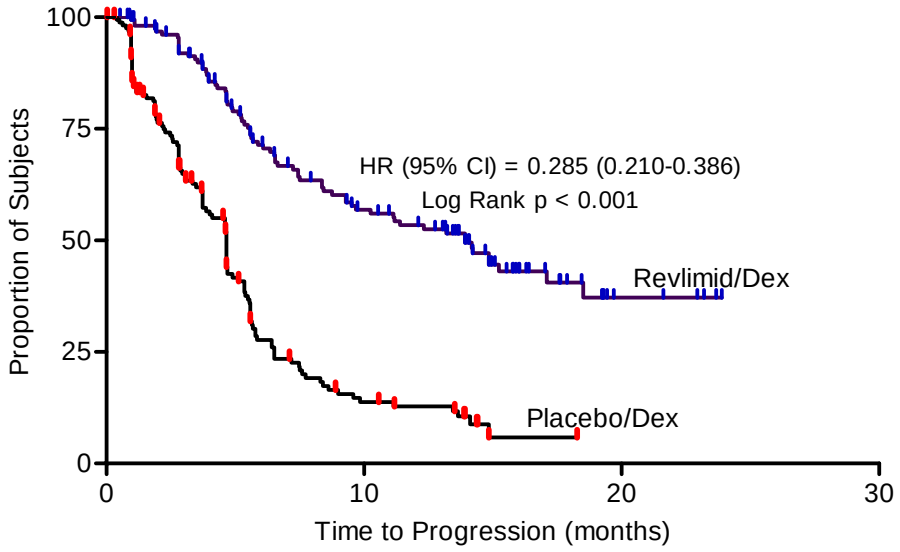
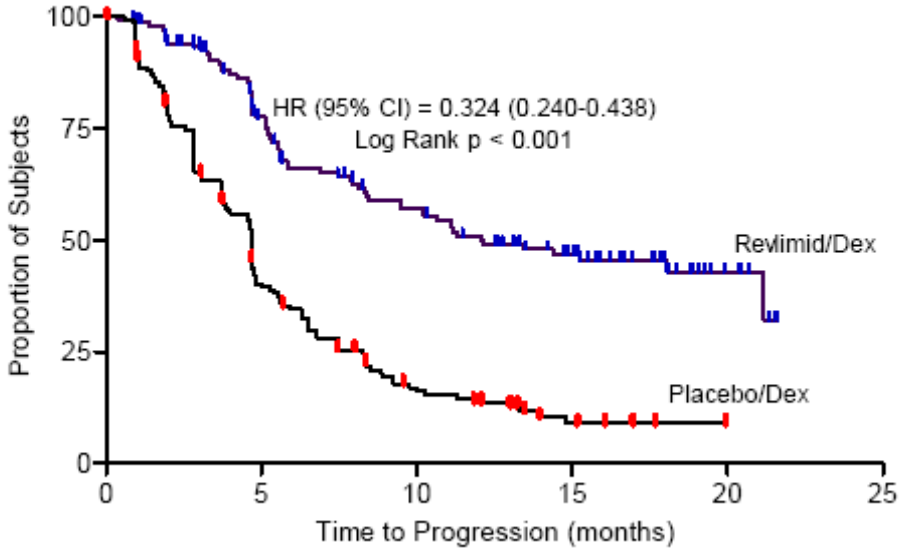


Figure 2: Kaplan-Meier Estimate of Time to Progression — Study 2



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

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

This major study enrolled 148 patients who had RBC transfusion dependent anemia. RBC transfusion dependence was defined as having received ≥ 2 units of RBCs within 8 weeks prior to study treatment. The study enrolled patients with absolute neutrophil counts (ANC) ≥ 500/mm^3, platelet counts ≥ 50,000/mm^3, serum creatinine ≤ 2.5 mg/dL, serum SGOT/AST or SGPT/ALT ≤ 3.0 x upper limit of normal (ULN), and serum direct bilirubin ≤ 2.0 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 11.

Table 11: Baseline Demographic and Disease-Related Characteristics in the MDS Study

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

[a] IPSS Risk Category: Low (combined score = 0), Intermediate-1 (combined score = 0.5 to 1.0), Intermediate-2 (combined score = 1.5 to 2.0), High (combined score ≥ 2.5); Combined score = (Marrow blast score + Karyotype score + Cytopenia score)

[b] French-American-British (FAB) classification of MDS.

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

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

Ninety percent of patients who achieved a transfusion benefit did so by completion of three months in the study.

RBC transfusion independence rates were unaffected by age or gender.

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

15 REFERENCES

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.

2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html

3. American Society of Health-System Pharmacists. ASHP Guidelines on Handling Hazardous Drugs: *Am J Health-Syst Pharm*. 2006;63:1172-1193.

4. Polovich M., White JM, Kelleher LO (eds). Chemotherapy and biotherapy guidelines and recommendations for practice (2nd ed.) 2005. Pittsburgh, PA: Oncology Nursing Society.

16. HOW SUPPLIED/STORAGE AND HANDLING

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

Procedures for the proper handling and disposal of anticancer drugs should be considered. Several guidelines on the subject have been published.[1-4]

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)

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)

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

Dispense no more than a 28-day supply.

17. PATIENT COUNSELING INFORMATION

See Medication Guide (17.4)

17.1 Importance of Preventing Pregnancy

Females of Childbearing Potential

Patients must be counseled on lenalidomide's potential risk of teratogenicity due to its structural similarity to thalidomide and data from an embryofetal development study showing treatment with lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy.

REVLIMID treatment should only be initiated in females of childbearing potential following a negative pregnancy test. Females of childbearing potential must be informed 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 therapy 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 condom, diaphragm and cervical cap. Patient must be instructed 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. The patient understands that if her doctor is not available, she can call 1-888-668-2528 for information on emergency contraception *[see Use in Specific Populations (8.1)]*.

REVLIMID treatment should only be initiated in a female not of childbearing potential if she confirms that she is not now pregnant, nor of childbearing potential as she has been postmenopausal naturally for at least 24 months (been through the change of life); or she has had a hysterectomy or bilateral oophorectomy. The patient or guardian certifies that a prepubertal female child is not now pregnant, nor is of childbearing potential as menstruation has not yet begun, and/or the child will not be engaging in heterosexual sexual contact for at least 4 weeks before REVLIMID therapy, during therapy, during therapy interruption and for at least 4 weeks after stopping REVLIMID therapy.

REVLIMID treatment should only be initiated in men who agree to either completely abstain from sexual contact with women who are pregnant or able to become pregnant, or use a latex condom every time he engages in any sexual contact with women who are pregnant or may become pregnant. The patient should inform his doctor if he has had unprotected sexual contact with a woman who can become pregnant. He understands that if his doctor is not available, he can call 1-888-668-2528 for information on emergency contraception.

17.2 Hematologic Toxicity

REVLIMID is associated with significant neutropenia and thrombocytopenia *[see Boxed Warnings and Warnings and Precautions (5.2)]*

17.3 Deep Vein Thrombosis and Pulmonary Embolism

REVLIMID/dexamethasone has demonstrated significant increased risk of DVT and PE in patients with multiple myeloma *[see Boxed Warnings and Warning and Precautions (5.3)]*

17.4 MEDICATION GUIDE

MEDICATION GUIDE
REVLIMID (rev-li-mid)
(lenalidomide)
Capsules

Read the Medication Guide that comes with REVLIMID before you start taking it and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

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 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 women. REVLIMID has harmed unborn animals in animal testing.

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

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

  It is not known if REVLIMID passes into semen, so:

  - Males, including those who have had a vasectomy, must use a latex condom during any sexual contact with a pregnant female or a female that can become

pregnant while taking REVLIMID, during any breaks (interruptions) in your treatment with REVLIMID, and for 4 weeks after stopping REVLIMID. (If you or your partner are allergic to latex, please consult with your healthcare provider)

- 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 patients. You may need a blood transfusion or certain medicines if your blood counts drop too low. If you are being treated for del 5q myelodysplastic syndromes (MDS) your blood counts should be checked weekly during the first 8 weeks of treatment with REVLIMID, and at least monthly thereafter. If you are being treated for multiple myeloma, your blood counts should be checked every 2 weeks for the first 12 weeks and then at least monthly thereafter.

A higher chance for blood clots in your veins and lungs. Call your healthcare provider or get medical help right away if you get any of these signs or symptoms:

- shortness of breath
- chest pain
- arm or leg swelling

What is REVLIMID?

REVLIMID is a prescription medicine taken by mouth to treat certain patients who have myelodysplastic syndromes (MDS). People with MDS have bone marrow that does not produce enough mature blood cells. This causes a lack of healthy blood cells that can function properly in the body. There are different types of 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.

REVLIMID is also used with dexamethasone to treat people with multiple myeloma who have already had another treatment. Multiple myeloma is a cancer of plasma cells. Plasma cells are found in the bone marrow. Normal plasma cells produce proteins called antibodies. Some antibodies can attack and kill disease causing germs. People with multiple myeloma may have low blood cell counts and immune problems giving them a higher chance for getting infections such as pneumonia. The may also have bone pain and breaks (fractures).

Who should not take REVLIMID?

- Do not take REVLIMID if you are pregnant, plan to become pregnant, or become pregnant during REVLIMID treatment. See "What is the most important information I should know about REVLIMID?"

- Do not take REVLIMID if you are allergic to anything in it. 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?

Tell your healthcare provider about all of your medical conditions, including if you:

- **are pregnant or breastfeeding.** REVLIMID must not be used by women who are pregnant or breastfeeding. See "What is the most important information I should know about REVLIMID?" It is not known if REVLIMID passes into your breast milk and harms your baby.

Tell your healthcare provider about all the medicines you take including prescription and non-prescription 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 RevAssist program. Before prescribing REVLIMID, your healthcare provider will:

- explain the RevAssist program to you
- have you sign the Patient-Physician Agreement Form

- Swallow REVLIMID capsules whole with water once a day. **Do not break, chew, or open your capsules.**

- 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 or poison control center 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, 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 condom during sexual contact with a pregnant female or a female who can become pregnant. (If you or your partner is allergic to latex, please consult with your healthcare provider.)

What should I avoid while taking REVLIMID?

- **Females: Do not get pregnant and do not breastfeed while taking REVLIMID. Males: Do not donate sperm,** See "What is the most important information I should I know about REVLIMID?", "Who should not take REVLIMID?", and "What should I avoid while taking REVLIMID?".

- **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.**

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

- **Serious skin reactions**. Serious skin reactions can happen with REVLIMID and may cause death. Call your healthcare provider right away if you have any skin reaction while taking REVLIMID.

- **Tumor lysis syndrome.** Metabolic complications that can occur during treatment of cancer and sometimes even without treatment. These complications are caused by the breakdown products of dying cancer cells and may include the following: changes to blood chemistry, high potassium, phosphorus, uric acid, and low calcium consequently leading to changes in kidney function, heart beat, seizures, and sometimes death.

Common side effects of REVLIMID are:

- diarrhea
- itching
- rash
- tiredness

These are not all the possible side effects of REVLIMID. Tell your healthcare provider about any side effect that bothers you or that does not go away.

Call your healthcare provider 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, 59°F to 86°F (15°C to 30°C).

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.

This Medication Guide provides a summary of the most important information about REVLIMID. 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 healthcare professionals. You can also call 1-888-423-5436 or visit www.REVLIMID.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 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.

Manufactured for Celgene Corporation

Summit, NJ 07901

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

RevPlyMG.00X XX/09