

LENALIDOMIDE- lenalidomide capsule
Teva Pharmaceuticals, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LENALIDOMIDE capsules, for oral use
Initial U.S. 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).
Lenalidomide capsules are available only through a restricted distribution program, called the Lenalidomide REMS program (5.2, 17).

HEMATOLOGIC TOXICITY. Lenalidomide capsules can cause significant neutropenia and thrombocytopenia (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 lenalidomide capsules with dexamethasone. Anti-thrombotic prophylaxis is recommended (5.4).

RECENT MAJOR CHANGES

Warnings and Precautions (5.1, 5.2) 8/2021
Warnings and Precautions (5.1, 5.11) 5/2022

INDICATIONS AND USAGE

Lenalidomide is a thalidomide analogue indicated for the treatment of adult 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:

- Lenalidomide capsules are not indicated and are not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials (1.6).

DOSAGE AND ADMINISTRATION

- MM combination therapy: 25 mg once daily orally on Days 1 to 21 of repeated 28-day cycles. (2.1).
- MDS: 10 mg once daily (2.2).
- MCL: 25 mg once daily orally on Days 1 to 21 of repeated 28-day cycles (2.3).
- Renal impairment: Adjust starting dose based on the creatinine clearance value (2.6).
- For concomitant therapy doses, see Full Prescribing Information (2.1, 14.1).

DOSAGE FORMS AND STRENGTHS

Capsules: 2.5 mg and 20 mg (3).

CONTRAINDICATIONS

- Pregnancy (Boxed Warning, 4.1, 5.1, 8.1).
- Demonstrated severe hypersensitivity to lenalidomide (4.2, 5.9, 5.15).

WARNINGS AND PRECAUTIONS

- Increased Mortality: serious and fatal cardiac adverse reactions occurred in patients with CLL treated with lenalidomide capsules (5.5).

- Second Primary Malignancies (SPM): Higher incidences of SPM were observed in controlled trials of patients with MM receiving lenalidomide capsules (5.6).
- Increased Mortality: Observed in patients with MM when pembrolizumab was added to dexamethasone and a thalidomide analogue (5.7).
- Hepatotoxicity: Hepatic failure including fatalities; monitor liver function. Stop lenalidomide capsules and evaluate if hepatotoxicity is suspected (5.8).
- Severe Cutaneous Reactions: Discontinue lenalidomide for severe reactions (5.9).
- Tumor lysis syndrome (TLS) including fatalities: Monitor patients at risk of TLS (i.e., those with high tumor burden) and take appropriate precautions (5.10).
- Tumor flare reaction: Serious tumor flare reactions, including fatal reactions, have occurred during investigational use of lenalidomide capsules for chronic lymphocytic leukemia and lymphoma (5.11).
- Impaired Stem Cell mobilization: A decrease in the number of CD34+ cells collected after treatment (> 4 cycles) with lenalidomide has been reported. Consider early referral to transplant center (5.12).
- Early mortality in MCL: Higher rate of early deaths have occurred in patients with MCL (5.14).
- Hypersensitivity: Monitor patients for potential hypersensitivity. Discontinue lenalidomide for angioedema and anaphylaxis (5.15).

-----**ADVERSE REACTIONS**-----

- MM: Most common adverse reactions (≥20%) include diarrhea, fatigue, anemia, constipation, neutropenia, leukopenia, peripheral edema, insomnia, muscle cramp/spasms, abdominal pain, back pain, nausea, asthenia, pyrexia, upper respiratory tract infection, bronchitis, nasopharyngitis, gastroenteritis, 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).
- Non-Hodgkin’s Lymphoma (NHL: MCL): Most common adverse reactions (≥15%) included neutropenia, thrombocytopenia, anemia, leukopenia, diarrhea, constipation, nausea, fatigue, pyrexia, cough, upper respiratory tract infection, and rash (6.1).

To report SUSPECTED ADVERSE REACTIONS contact Teva at 1-888-838-2872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----**DRUG INTERACTIONS**-----

- Digoxin: Monitor digoxin plasma levels periodically due to increased C_{max} and AUC with concomitant lenalidomide capsules therapy (7.1).
- Concomitant use of erythropoietin stimulating agents or estrogen containing therapies with lenalidomide capsules may increase the risk of thrombosis (7.2).

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

- Lactation: Advise not to breastfeed (8.2).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2022

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FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM

Embryo-Fetal Toxicity

Do not use lenalidomide capsules 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 lenalidomide treatment. Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after lenalidomide capsules treatment [see *Warnings and Precautions (5.1)*, and *Medication Guide (17)*]. To avoid embryo-fetal exposure to lenalidomide, lenalidomide capsules are only available through a restricted distribution program, the Lenalidomide REMS program (5.2).

Information about the Lenalidomide REMS program is available at www.lenalidomiderems.com or by calling the toll-free number 1-888-423-5436.

Hematologic Toxicity (Neutropenia and Thrombocytopenia)

Lenalidomide capsules 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

Lenalidomide capsules have 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 lenalidomide capsules 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

Lenalidomide capsules in combination with dexamethasone are indicated for the treatment of adult patients with multiple myeloma (MM).

1.2 Myelodysplastic Syndromes

Lenalidomide capsules are indicated for the treatment of adult 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

Lenalidomide capsules are indicated for the treatment of adult patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.

1.6 Limitations of Use

Lenalidomide capsules are not indicated and are not recommended for the treatment of patients with CLL outside of controlled clinical trials [see *Warnings and Precautions* (5.5)].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Multiple Myeloma

Lenalidomide Capsules Combination Therapy

The recommended starting dose of lenalidomide capsules is 25 mg orally once daily on Days 1 to 21 of repeated 28-day cycles in combination with dexamethasone. Refer to Section 14.1 for specific dexamethasone dosing. For patients greater than 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 auto-HSCT, treatment should continue until disease progression or unacceptable toxicity. For patients who are auto-HSCT-eligible, hematopoietic stem cell mobilization should occur within 4 cycles of a lenalidomide-containing therapy [see *Warnings and Precautions* (5.12)].

Dose Adjustments for Hematologic Toxicities During MM 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 lenalidomide capsules.

Table 1: Dose Adjustments for Hematologic Toxicities for MM

Platelet counts	
Thrombocytopenia in MM	
When Platelets	Recommended Course Days 1 to 21 of repeated 28-day cycle
Fall below 30,000/mcL	Interrupt lenalidomide capsules treatment, follow CBC weekly
Return to at least 30,000/mcL	Resume lenalidomide capsules at next lower dose. Do not dose below 2.5 mg daily

For each subsequent drop below 30,000/mcL	Interrupt lenalidomide capsules treatment
Return to at least 30,000/mcL	Resume lenalidomide capsules at next lower dose. Do not dose below 2.5 mg daily

Absolute Neutrophil counts (ANC)

Neutropenia in MM

When Neutrophils	Recommended Course Days 1 to 21 of repeated 28-day cycle
Fall below 1,000/mcL	Interrupt lenalidomide capsules treatment, follow CBC weekly
Return to at least 1,000/mcL and neutropenia is the only toxicity	Resume lenalidomide capsules at 25 mg daily or initial starting dose
Return to at least 1,000/mcL and if other toxicity	Resume lenalidomide capsules at next lower dose. Do not dose below 2.5 mg daily
For each subsequent drop below 1,000/mcL	Interrupt lenalidomide capsules treatment
Return to at least 1,000/mcL	Resume lenalidomide capsules at next lower dose. Do not dose below 2.5 mg daily

2.2 Recommended Dosage for Myelodysplastic Syndromes

The recommended starting dose of lenalidomide capsules is 10 mg daily. Treatment is continued or modified based upon clinical and laboratory findings. Continue treatment until disease progression or unacceptable toxicity.

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 is at least 100,000/mcL

When Platelets	Recommended Course
Fall below 50,000/mcL	Interrupt lenalidomide capsules treatment
Return to at least 50,000/mcL	Resume lenalidomide capsules at 5 mg daily

If baseline is below 100,000/mcL

When Platelets	Recommended Course
Fall to 50% of the baseline value	Interrupt lenalidomide capsules treatment
If baseline is at least 60,000/mcL and returns to at least 50,000/mcL	Resume lenalidomide capsules at 5 mg daily
If baseline is below 60,000/mcL and returns to at least 30,000/mcL	Resume lenalidomide capsules at 5 mg daily

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

When Platelets	Recommended Course
Fall below 30,000/mcL or below 50,000/mcL with platelet transfusions	Interrupt lenalidomide capsules treatment
Return to at least 30,000/mcL (without hemostatic failure)	Resume lenalidomide capsules 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
Fall below 30,000/mcL or below 50,000/mcL with platelet transfusions	Interrupt lenalidomide capsules treatment
Return to at least 30,000/mcL (without hemostatic failure)	Resume lenalidomide capsules at 2.5 mg daily

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

Absolute Neutrophil counts (ANC)

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

If baseline ANC is at least 1,000/mcL	
When Neutrophils	Recommended Course
Fall below 750/mcL	Interrupt lenalidomide capsules treatment
Return to at least 1,000/mcL	Resume lenalidomide capsules at 5 mg daily
If baseline ANC is below 1,000/mcL	
When Neutrophils	Recommended Course
Fall below 500/mcL	Interrupt lenalidomide capsules treatment
Return to at least 500/mcL	Resume lenalidomide capsules at 5 mg daily

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

When Neutrophils	Recommended Course
Fall below 500/mcL for at least 7 days or below 500/mcL associated with fever (at least 38.5°C)	Interrupt lenalidomide capsules treatment
Return to at least 500/mcL	Resume lenalidomide capsules 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
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Fall below 500/mcL for at least 7 days or below 500/mcL associated with fever (at least 38.5°C)	Interrupt lenalidomide capsules treatment
Return to at least 500/mcL	Resume lenalidomide capsules at 2.5 mg daily

2.3 Recommended Dosage for Mantle Cell Lymphoma

The recommended starting dose of lenalidomide capsules is 25 mg/day orally on Days 1 to 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 lenalidomide capsules.

Platelet counts

Thrombocytopenia during treatment in MCL

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

Absolute Neutrophil counts (ANC)

Neutropenia during treatment in MCL

When Neutrophils	Recommended Course
Fall below 1,000/mcL for at least 7 days OR Falls below 1,000/mcL with an associated temperature at least 38.5°C OR Falls below 500/mcL	Interrupt lenalidomide capsules treatment and follow CBC weekly
Return to at least 1,000/mcL	Resume lenalidomide capsules at 5 mg less than the previous dose. Do not dose below 5 mg daily

2.5 Dosage Modifications for Non-Hematologic Adverse Reactions

For non-hematologic Grade 3/4 toxicities judged to be related to lenalidomide capsules,

hold treatment and restart at the physician's discretion at next lower dose level when toxicity has resolved to Grade 2 or below.

Permanently discontinue lenalidomide capsules for angioedema, anaphylaxis, Grade 4 rash, skin exfoliation, bullae, or any other severe dermatologic reactions [see *Warnings and Precautions* (5.9, 5.15)].

2.6 Recommended Dosage for Patients with Renal Impairment

The recommendations for dosing patients with renal impairment are shown in the following table [see *Clinical Pharmacology* (12.3)].

Table 3: Dose Adjustments for Patients with Renal Impairment

Renal Function (Cockcroft-Gault)	Dose in Lenalidomide Capsules Combination Therapy for MM and MCL	Dose in Lenalidomide Capsules for MDS
CLcr 30 to 60 mL/min	10 mg once daily	5 mg once daily
CLcr below 30 mL/min (not requiring dialysis)	15 mg every other day	2.5 mg once daily
CLcr below 30 mL/min (requiring dialysis)	5 mg once daily. On dialysis days, administer the dose following dialysis.	2.5 mg once daily. On dialysis days, administer the dose following dialysis.

Lenalidomide Capsules Combination Therapy for MM: For CLcr of 30 to 60 mL/min, consider escalating the dose to 15 mg after 2 cycles if the patient tolerates the 10 mg dose of lenalidomide without dose-limiting toxicity.

Lenalidomide Capsules Therapy for MCL and MDS: Base subsequent lenalidomide capsules dose increase or decrease on individual patient treatment tolerance [see *Dosage and Administration* (2.1 to 2.3)].

2.7 Administration

Advise patients to take lenalidomide capsules orally at about the same time each day, either with or without food. Advise patients to swallow lenalidomide capsules whole with water and not to open, break, or chew them.

3 DOSAGE FORMS AND STRENGTHS

Capsules:

- 2.5 mg white capsules printed with "NAT" on cap and "2.5mg" on body of the capsule in black ink.
- 20 mg green/blue capsules printed with "NAT" on cap and "20 mg" on body of the capsule in black ink.

4 CONTRAINDICATIONS

4.1 Pregnancy

Lenalidomide capsules 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 risk to a fetus [see *Warnings and Precautions (5.1, 5.2), Use in Special Populations (8.1, 8.3)*].

4.2 Severe Hypersensitivity Reactions

Lenalidomide capsules are contraindicated in patients who have demonstrated severe hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide [see *Warnings and Precautions (5.9, 5.15)*].

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Lenalidomide 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.

Lenalidomide capsules are only available through the Lenalidomide REMS 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 lenalidomide capsules 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 lenalidomide capsules, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of lenalidomide therapy.

Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10 to 14 days and the second test within 24 hours prior to prescribing lenalidomide therapy and then weekly during the first month, then monthly thereafter in females with regular menstrual cycles or every 2 weeks in females with irregular menstrual cycles [see *Use in Specific Populations (8.3)*].

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 lenalidomide capsules and for up to 4 weeks after discontinuing lenalidomide capsules, even if they have undergone a successful vasectomy. Male patients taking lenalidomide capsules must not donate sperm and for up to 4 weeks after discontinuing lenalidomide capsules [see *Use in Specific Populations (8.3)*].

Blood Donation

Patients must not donate blood during treatment with lenalidomide capsules and for 4 weeks following discontinuation of the drug because the blood might be given to a

pregnant female patient whose fetus must not be exposed to lenalidomide.

5.2 Lenalidomide REMS Program

Because of the embryo-fetal risk [see *Warnings and Precautions (5.1)*], lenalidomide capsules are available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS), the **Lenalidomide REMS** program.

Required components of the **Lenalidomide REMS** program include the following:

- Prescribers must be certified with the **Lenalidomide 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 (8.3)*] and males must comply with contraception requirements [see *Use in Specific Populations (8.3)*].
- Pharmacies must be certified with the **Lenalidomide REMS** program, must only dispense to patients who are authorized to receive lenalidomide capsules and comply with REMS requirements.

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

5.3 Hematologic Toxicity

Lenalidomide capsules 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 lenalidomide capsules should have their complete blood counts assessed periodically as described below [see *Dosage and Administration (2.1, 2.2, 2.3)*].

Monitor complete blood counts (CBC) in patients taking lenalidomide capsules in combination with dexamethasone for MM 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)*]. In trials for another indication, Grade 3 or 4 neutropenia was reported in up to 59% of lenalidomide capsules-treated patients and Grade 3 or 4 thrombocytopenia in up to 38% of lenalidomide capsules-treated patients.

Monitor complete blood counts (CBC) in patients taking lenalidomide capsules for MDS 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 to 411 days), and the median time to documented recovery was 17 days (range, 2 to 170 days). In the 54% of patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was 28 days (range, 8 to 290 days), and the median time to documented recovery was 22 days (range, 5 to 224 days) [see *Boxed Warning and Dosage and Administration (2.2)*].

Monitor complete blood counts (CBC) in patients taking lenalidomide capsules for MCL weekly for the first cycle (28 days), every 2 weeks during cycles 2 to 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 (VTE [DVT and PE]) and arterial thromboembolic events (ATE, myocardial infarction and stroke) are increased in patients treated with lenalidomide.

A significantly increased risk of DVT (7.4%) and of PE (3.7%) occurred in patients with MM after at least one prior therapy who were treated with lenalidomide 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 MM after at least one prior therapy who were treated with lenalidomide capsules 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 MM who were treated with lenalidomide capsules 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 4.3 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 lenalidomide capsules [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 lenalidomide capsules 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 lenalidomide capsules 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 to 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 lenalidomide capsules treatment arm. Lenalidomide 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 MM receiving lenalidomide capsules, an increase of hematologic plus solid tumor second primary malignancies (SPM) notably AML and MDS have been observed. An increase in hematologic SPM including AML and MDS occurred in 5.3% of patients with NDMM receiving lenalidomide capsules in combination with oral melphalan compared with 1.3% of patients receiving melphalan without lenalidomide capsules. The frequency of AML and MDS cases in patients with NDMM treated with lenalidomide capsules in combination with dexamethasone without melphalan was 0.4%.

In a study for another indication, hematologic SPM occurred in 7.5% of patients compared to 3.3% in patients receiving placebo. The incidence of hematologic plus solid tumor (excluding squamous cell carcinoma and basal cell carcinoma) SPM was 14.9%, compared to 8.8% in patients receiving placebo with a median follow-up of 91.5 months. Non-melanoma skin cancer SPM, including squamous cell carcinoma and basal cell carcinoma, occurred in 3.9% of patients receiving lenalidomide capsules maintenance, compared to 2.6% in the placebo arm.

In patients with relapsed or refractory MM treated with lenalidomide capsules/dexamethasone, the incidence of hematologic plus solid tumor (excluding squamous cell carcinoma and basal cell carcinoma) SPM was 2.3% versus 0.6% in the dexamethasone alone arm. Non-melanoma skin cancer SPM, including squamous cell carcinoma and basal cell carcinoma, occurred in 3.1% of patients receiving lenalidomide capsules/dexamethasone, compared to 0.6% in the dexamethasone alone arm.

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

5.7 Increased Mortality in Patients with MM When Pembrolizumab Is Added to a Thalidomide Analogue and Dexamethasone

In two randomized clinical trials in patients with MM, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with MM with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

5.8 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 MM 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 lenalidomide upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

5.9 Severe Cutaneous Reactions

Severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis.

These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive lenalidomide capsules. Consider lenalidomide capsules interruption or discontinuation for Grade 2-3 skin rash. Permanently discontinue lenalidomide capsules for Grade 4 rash, exfoliative or bullous rash, or for other severe cutaneous reactions such as SJS, TEN or DRESS [see *Dosage and Administration (2.5)*].

5.10 Tumor Lysis Syndrome

Fatal instances of tumor lysis syndrome (TLS) have been reported during treatment with lenalidomide. The patients at risk of TLS are those with high tumor burden prior to treatment. Monitor patients at risk closely and take appropriate preventive approaches.

5.11 Tumor Flare Reaction

Tumor flare reaction (TFR), including fatal reactions, have occurred during investigational use of lenalidomide for CLL and lymphoma, and is characterized by tender lymph node swelling, low grade fever, pain and rash. Lenalidomide is not indicated and not recommended for use in CLL outside of controlled clinical trials.

Monitoring and evaluation for 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. In a separate MCL phase 2 trial, one case of TFR resulted in a fatal outcome.

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 \leq 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.

5.12 Impaired Stem Cell Mobilization

A decrease in the number of CD34+ cells collected after treatment (> 4 cycles) with lenalidomide has been reported. In patients who are auto-HSCT 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 lenalidomide-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.

5.13 Thyroid Disorders

Both hypothyroidism and hyperthyroidism have been reported [see *Adverse Reactions (6.2)*]. Measure thyroid function before start of lenalidomide capsules treatment and during therapy.

5.14 Early Mortality in Patients with MCL

In another MCL study, there was an increase in early deaths (within 20 weeks), 12.9% in the lenalidomide arm versus 7.1% in the control arm. On exploratory multivariate analysis, risk factors for early deaths include high tumor burden, MIPI score at diagnosis, and high WBC at baseline ($\geq 10 \times 10^9/L$).

5.15 Hypersensitivity

Hypersensitivity, including angioedema, anaphylaxis, and anaphylactic reactions to

lenalidomide capsules have been reported. Permanently discontinue lenalidomide capsules for angioedema and anaphylaxis [see *Dosage and Administration (2.2)*].

6 ADVERSE REACTIONS

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

- Embryo-Fetal Toxicity [see *Boxed Warning, Warnings and Precautions (5.1, 5.2)*]
- Hematologic Toxicity [see *Boxed Warning, Warnings and Precautions (5.3)*]
- Venous and Arterial Thromboembolism [see *Boxed Warning, 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)*]
- Increased Mortality in Patients with MM When Pembrolizumab Is Added to a Thalidomide Analogue and Dexamethasone [see *Warnings and Precautions (5.7)*]
- Hepatotoxicity [see *Warnings and Precautions (5.8)*]
- Severe Cutaneous Reactions [see *Warnings and Precautions (5.9)*]
- Tumor Lysis Syndrome [see *Warnings and Precautions (5.10)*]
- Tumor Flare Reactions [see *Warnings and Precautions (5.11)*]
- Impaired Stem Cell Mobilization [see *Warnings and Precautions (5.12)*]
- Thyroid Disorders [see *Warnings and Precautions (5.13)*]
- Early Mortality in Patients with MCL [see *Warnings and Precautions (5.14)*]
- Hypersensitivity [see *Warnings and Precautions (5.15)*]

6.1 Clinical Trials Experience

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.

Newly Diagnosed MM – Lenalidomide Capsules Combination Therapy:

Data were evaluated from 1613 patients in a large phase 3 study who received at least one dose of lenalidomide 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 lenalidomide were infection events (28.8%); overall, the median time to the first dose interruption of lenalidomide was 7 weeks. The most common adverse reactions leading to dose reduction of lenalidomide in the Rd Continuous arm were hematologic events (10.7%); overall, the median time to the first dose reduction of lenalidomide was 16 weeks. In the Rd Continuous arm, the most common adverse reactions leading to discontinuation of lenalidomide 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% and Grade 3/4 Adverse Reactions in ≥1% of Patients with MM in the Rd Continuous or Rd18 Arms*

Body System Adverse Reaction	All Adverse Reactions ^a			Grade 3/4 Adverse Reactions ^b		
	Rd Continuous (N=532)	Rd18 (N=540)	MPT (N=541)	Rd Continuous (N=532)	Rd18 (N=540)	MPT (N=541)
General disorders and administration site conditions						
Fatigue [%]	173 (33)	177 (33)	154 (28)	39 (7)	46 (9)	31 (6)
Asthenia	150 (28)	123 (23)	124 (23)	41 (8)	33 (6)	32 (6)
Pyrexia ^c	114 (21)	102 (19)	76 (14)	13 (2)	7 (1)	7 (1)
Non-cardiac chest pain ^f	29 (5)	31 (6)	18 (3)	<1%	< 1%	< 1%
Gastrointestinal disorders						
Diarrhea	242 (45)	208 (39)	89 (16)	21 (4)	18 (3)	8 (1)
Abdominal pain ^{%f}	109 (20)	78 (14)	60 (11)	7 (1)	9 (2)	< 1%
Dyspepsia ^f	57 (11)	28 (5)	36 (7)	<1%	< 1%	0 (0)
Musculoskeletal and connective tissue disorders						
Back pain ^c	170 (32)	145 (27)	116 (21)	37 (7)	34 (6)	28 (5)
Muscle spasms ^f	109 (20)	102 (19)	61 (11)	< 1%	< 1%	< 1%
Arthralgia ^f	101 (19)	71 (13)	66 (12)	9 (2)	8 (1)	8 (1)
Bone pain ^f	87 (16)	77 (14)	62 (11)	16 (3)	15 (3)	14 (3)
Pain in extremity ^f	79 (15)	66 (12)	61 (11)	8 (2)	8 (1)	7 (1)
Musculoskeletal pain ^f	67 (13)	59 (11)	36 (7)	< 1%	< 1%	< 1%
Musculoskeletal chest pain ^f	60 (11)	51 (9)	39 (7)	6 (1)	< 1%	< 1%
Muscular weakness ^f	43 (8)	35 (6)	29 (5)	< 1%	8 (1)	< 1%
Neck pain ^f	40 (8)	19 (4)	10 (2)	< 1%	< 1%	< 1%
Infections and infestations						
Bronchitis ^c	90 (17)	59 (11)	43 (8)	9 (2)	6 (1)	< 1%
Nasopharyngitis ^f	80 (15)	54 (10)	33 (6)	0 (0)	0 (0)	0 (0)
Urinary tract infection ^f	76 (14)	63 (12)	41 (8)	8 (2)	8 (1)	< 1%
Upper respiratory tract infection ^{c% f}	69 (13)	53 (10)	31 (6)	< 1%	8 (1)	< 1%
Pneumonia ^{c@}	93 (17)	87 (16)	56 (10)	60 (11)	57 (11)	41 (8)
Respiratory tract infection [%]	35 (7)	25 (5)	21 (4)	7 (1)	< 1%	< 1%
Influenza ^f	33 (6)	23 (4)	15 (3)	< 1%	< 1%	0 (0)
Gastroenteritis ^f	32 (6)	17 (3)	13 (2)	0 (0)	< 1%	< 1%
Lower respiratory tract infection	29 (5)	14 (3)	16 (3)	10 (2)	< 1%	< 1%
Rhinitis ^f	29 (5)	24 (4)	14 (3)	0 (0)	0 (0)	0 (0)
Cellulitis ^c	< 5%	< 5%	< 5%	8 (2)	< 1%	< 1%

Sepsis ^{c@}	33 (6)	26 (5)	18 (3)	26 (5)	20 (4)	13 (2)
Nervous system disorders						
Headache ^f	75 (14)	52 (10)	56 (10)	< 1%	< 1%	< 1%
Dysgeusia ^f	39 (7)	45 (8)	22 (4)	< 1%	0 (0.0)	< 1%
Blood and lymphatic system disorders^d						
Anemia	233 (44)	193 (36)	229 (42)	97 (18)	85 (16)	102 (19)
Neutropenia	186 (35)	178 (33)	328 (61)	148 (28)	143 (26)	243 (45)
Thrombocytopenia	104 (20)	100 (19)	135 (25)	44 (8)	43 (8)	60 (11)
Febrile neutropenia	7 (1)	17 (3)	15 (3)	6 (1)	16 (3)	14 (3)
Pancytopenia	< 1%	6 (1)	7 (1)	< 1%	< 1%	< 1%
Respiratory, thoracic and mediastinal disorders						
Cough ^f	121 (23)	94 (17)	68 (13)	< 1%	< 1%	< 1%
Dyspnea ^{c,e}	117 (22)	89 (16)	113 (21)	30 (6)	22 (4)	18 (3)
Epistaxis ^f	32 (6)	31 (6)	17 (3)	< 1%	< 1%	0 (0)
Oropharyngeal pain ^f	30 (6)	22 (4)	14 (3)	0 (0)	0 (0)	0 (0)
Dyspnea exertional ^e	27 (5)	29 (5)	< 5%	6 (1)	< 1%	0 (0)
Metabolism and nutrition disorders						
Decreased appetite	123 (23)	115 (21)	72 (13)	14 (3)	7 (1)	< 1%
Hypokalemia [%]	91 (17)	62 (11)	38 (7)	35 (7)	20 (4)	11 (2)
Hyperglycemia	62 (12)	52 (10)	19 (4)	28 (5)	23 (4)	9 (2)
Hypocalcemia	57 (11)	56 (10)	31 (6)	23 (4)	19 (4)	8 (1)
Dehydration [%]	25 (5)	29 (5)	17 (3)	8 (2)	13 (2)	9 (2)
Gout ^e	< 5%	< 5%	< 5%	8 (2)	0 (0)	0 (0)
Diabetes mellitus ^{% e}	< 5%	< 5%	< 5%	8 (2)	< 1%	< 1%
Hypophosphatemia ^e	< 5%	< 5%	< 5%	7 (1)	< 1%	< 1%
Hyponatremia ^{% e}	< 5%	< 5%	< 5%	7 (1)	13 (2)	6 (1)
Skin and subcutaneous tissue disorders						
Rash	139 (26)	151 (28)	105 (19)	39 (7)	38 (7)	33 (6)
Pruritus ^f	47 (9)	49 (9)	24 (4)	< 1%	< 1%	< 1%
Psychiatric disorders						
Insomnia	147 (28)	127 (24)	53 (10)	< 1%	6 (1)	0 (0)
Depression	58 (11)	46 (9)	30 (6)	10 (2)	< 1%	< 1%
Vascular disorders						
Deep vein thrombosis ^{c %}	55 (10)	39 (7)	22 (4)	30 (6)	20 (4)	15 (3)
Hypotension ^{c %}	51 (10)	35 (6)	36 (7)	11 (2)	8 (1)	6 (1)
Injury, Poisoning, and Procedural Complications						
Fall ^f	43 (8)	25 (5)	25 (5)	< 1%	6 (1)	6 (1)
Contusion ^f	33 (6)	24 (4)	15 (3)	< 1%	< 1%	0 (0)
Eye disorders						
Cataract	73 (14)	31 (6)	< 1%	31 (6)	14 (3)	< 1%
Cataract subcapsular ^e	< 5%	< 5%	< 5%	7 (1)	0 (0)	0 (0)
Investigations						
Weight decreased	72 (14)	78 (14)	48 (9)	11 (2)	< 1%	< 1%
Cardiac disorders						
Atrial fibrillation ^c	37 (7)	25 (5)	25 (5)	13 (2)	9 (2)	6 (1)
Myocardial infarction (including acute) ^{c,e}	< 5%	< 5%	< 5%	10 (2)	< 1%	< 1%
Renal and Urinary disorders						
Renal failure	10 (0)	51 (10)	37 (7)	28 (5)	33 (6)	20 (5)

(including acute) ^{c@,f}	43 (3)	34 (10)	37 (11)	28 (3)	33 (6)	23 (3)
Neoplasms benign, malignant and unspecified (Including cysts and polyps)						
Squamous cell carcinoma ^{c e}	< 5%	< 5%	< 5%	8 (2)	< 1%	0 (0)
Basal cell carcinoma ^{c e,f}	< 5%	< 5%	< 5%	< 1%	< 1%	0 (0)

Note: A subject with multiple occurrences of an adverse reaction is counted only once under the applicable Body System/Adverse Reaction.

^a All treatment-emergent adverse events in at least 5% of subjects in the Rd Continuous or Rd18 Arms and at least a 2% higher frequency (%) in either the Rd Continuous or Rd18 Arms compared to the MPT Arm.

^b All grade 3 or 4 treatment-emergent adverse events in at least 1% of subjects in the Rd Continuous or Rd18 Arms and at least a 1% higher frequency (%) in either the Rd Continuous or Rd18 Arms compared to the MPT Arm.

^c Serious treatment-emergent adverse events in at least 1% of subjects in the Rd Continuous or Rd18 Arms and at least a 1% higher frequency (%) in either the Rd Continuous or Rd18 Arms compared to the MPT Arm.

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

^e Footnote "a" not applicable.

^f Footnote "b" not applicable.

@ - adverse reactions in which at least one resulted in a fatal outcome.

% - 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).

* Adverse reactions included in 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 generalized, 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 lenalidomide/dexamethasone (353 patients) or placebo/dexamethasone (350 patients).

In the lenalidomide/dexamethasone treatment group, 269 patients (76%) had at least one dose interruption with or without a dose reduction of lenalidomide 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 lenalidomide/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 lenalidomide/dexamethasone compared to placebo/dexamethasone.

Tables 6, 7, and 8 summarize the adverse reactions reported for lenalidomide/dexamethasone and placebo/dexamethasone groups.

Table 6: Adverse Reactions Reported in $\geq 5\%$ of Patients and with a $\geq 2\%$ Difference in Proportion of Patients with MM between the Lenalidomide/dexamethasone and Placebo/dexamethasone Groups

Body System Adverse Reaction	Lenalidomide/Dex (N=353) n (%)	Placebo/Dex (N=350) n (%)
Blood and lymphatic system disorders		
Neutropenia ^o	149 (42)	22 (6)
Anemia [@]	111 (31)	83 (24)
Thrombocytopenia [@]	76 (22)	37 (11)
Leukopenia	28 (8)	4 (1)
Lymphopenia	19 (5)	5 (1)
General disorders and administration site conditions		
Fatigue	155 (44)	146 (42)
Pyrexia	97 (27)	82 (23)
Peripheral edema	93 (26)	74 (21)
Chest pain	29 (8)	20 (6)
Lethargy	24 (7)	8 (2)
Gastrointestinal disorders		
Constipation	143 (41)	74 (21)
Diarrhea [@]	136 (39)	96 (27)
Nausea [@]	92 (26)	75 (21)
Vomiting [@]	43 (12)	33 (9)
Abdominal pain [@]	35 (10)	22 (6)
Dry mouth	25 (7)	13 (4)
Musculoskeletal and connective tissue disorders		
Muscle cramp	118 (33)	74 (21)
Back pain	91 (26)	65 (19)
Bone pain	48 (14)	39 (11)
Pain in limb	42 (12)	32 (9)
Nervous system disorders		
Dizziness	82 (23)	59 (17)
Tremor	75 (21)	26 (7)
Dysgeusia	54 (15)	34 (10)
Hypoesthesia	36 (10)	25 (7)
Neuropathy ^a	23 (7)	13 (4)
Respiratory, thoracic and mediastinal disorders		
Dyspnea	83 (24)	60 (17)
Nasopharyngitis	62 (18)	31 (9)
Pharyngitis	48 (14)	33 (9)
Bronchitis	40 (11)	30 (9)
Infections^b and infestations		
Upper respiratory tract infection	87 (25)	55 (16)
Pneumonia [@]	48 (14)	29 (8)
Urinary tract infection	30 (8)	19 (5)
Sinusitis	26 (7)	16 (5)
Skin and subcutaneous system disorders		
Rash ^c	75 (21)	33 (9)

Sweating increased	35 (10)	25 (7)
Dry skin	33 (9)	14 (4)
Pruritus	27 (8)	18 (5)
Metabolism and nutrition disorders		
Anorexia	55 (16)	34 (10)
Hypokalemia	48 (14)	21 (6)
Hypocalcemia	31 (9)	10 (3)
Appetite decreased	24 (7)	14 (4)
Dehydration	23 (7)	15 (4)
Hypomagnesemia	24 (7)	10 (3)
Investigations		
Weight decreased	69 (20)	52 (15)
Eye disorders		
Blurred vision	61 (17)	40 (11)
Vascular disorders		
Deep vein thrombosis [%]	33 (9)	15 (4)
Hypertension	28 (8)	20 (6)
Hypotension	25 (7)	15 (4)

Table 7: Grade 3/4 Adverse Reactions Reported in $\geq 2\%$ Patients and with a $\geq 1\%$ Difference in Proportion of Patients with MM between the Lenalidomide/dexamethasone and Placebo/dexamethasone groups

Body System Adverse Reaction	Lenalidomide/Dex (N=353) n (%)	Placebo/Dex (N=350) n (%)
Blood and lymphatic system disorders		
Neutropenia [%]	118 (33)	12 (3)
Thrombocytopenia [@]	43 (12)	22 (6)
Anemia [@]	35 (10)	20 (6)
Leukopenia	14 (4)	< 1%
Lymphopenia	10 (3)	4 (1)
Febrile neutropenia [%]	8 (2)	0 (0)
General disorders and administration site conditions		
Fatigue	23 (7)	17 (5)
Vascular disorders		
Deep vein thrombosis [%]	29 (8)	12 (3)
Infections and infestations		
Pneumonia [@]	30 (8)	19 (5)
Urinary tract infection	5 (1)	< 1%
Metabolism and nutrition disorders		
Hypokalemia	17 (5)	5 (1)
Hypocalcemia	13 (4)	6 (2)
Hypophosphatemia	9 (3)	0 (0)
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism [@]	14 (4)	< 1%
Respiratory distress [@]	4 (1)	0 (0)
Musculoskeletal and connective tissue disorders		
Muscle weakness	20 (6)	10 (3)
Gastrointestinal disorders		
Diarrhea [@]	11 (3)	4 (1)

Constipation	7 (2)	< 1%
Nausea [@]	6 (2)	< 1%
Cardiac disorders		
Atrial fibrillation [@]	13 (4)	4 (1)
Tachycardia	6 (2)	< 1%
Cardiac failure congestive [@]	5 (1)	< 1%
Nervous system disorders		
Syncope	10 (3)	< 1%
Dizziness	7 (2)	< 1%
Eye disorders		
Cataract	6 (2)	< 1%
Cataract unilateral	5 (1)	0 (0)
Psychiatric disorder		
Depression	10 (3)	6 (2)

Table 8: Serious Adverse Reactions Reported in $\geq 1\%$ Patients and with a $\geq 1\%$ Difference in Proportion of Patients with MM between the Lenalidomide/dexamethasone and Placebo/dexamethasone Groups

Body System Adverse Reaction	Lenalidomide/Dex (N=353) n (%)	Placebo/Dex (N=350) n (%)
Blood and lymphatic system disorders		
Febrile neutropenia [%]	6 (2)	0 (0)
Vascular disorders		
Deep vein thrombosis [%]	26 (7)	11 (3)
Infections and infestations		
Pneumonia [@]	33 (9)	21 (6)
Respiratory, thoracic, and mediastinal disorders		
Pulmonary embolism [@]	13 (4)	< 1%
Cardiac disorders		
Atrial fibrillation [@]	11 (3)	< 1%
Cardiac failure congestive [@]	5 (1)	0 (0)
Nervous system disorders		
Cerebrovascular accident [@]	7 (2)	< 1%
Gastrointestinal disorders		
Diarrhea [@]	6 (2)	< 1%
Musculoskeletal and connective tissue disorders		
Bone pain	4 (1)	0 (0)

For Tables 6, 7 and 8 above:

[@] - adverse reactions in which at least one resulted in a fatal outcome.

[%] - 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 lenalidomide/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 lenalidomide/dexamethasone vs. placebo/dexamethasone.

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

VTE and ATE are increased in patients treated with lenalidomide capsules.

Deep vein thrombosis (DVT) was reported as a serious (7.4%) or severe (8.2%) adverse drug reaction at a higher rate in the lenalidomide/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 lenalidomide 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 lenalidomide/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 lenalidomide/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 lenalidomide/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 lenalidomide/dexamethasone group compared to 0.9% and 0.9% respectively in the placebo/dexamethasone group. Discontinuation due to stroke (CVA) was 1.4% in lenalidomide/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 $\geq 1\%$ 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 lenalidomide in the del 5q MDS clinical study. At least one adverse reaction was reported in all of the 148 patients who were treated with the 10 mg starting dose of lenalidomide capsules. The most frequently reported adverse reactions 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 reactions. The next most common adverse reactions observed were diarrhea (48.6%; 72/148), pruritus (41.9%; 62/148), rash (35.8%; 53/148) and fatigue (31.1%; 46/148). Table 9 summarizes the adverse reactions that were reported in $\geq 5\%$ of the lenalidomide treated patients in the del 5q MDS clinical study. Table 10 summarizes the most frequently observed Grade 3 and Grade 4 adverse reactions regardless of relationship to treatment with lenalidomide. In the single-arm studies conducted, it is often not possible to distinguish adverse reactions that are drug-related and those that reflect the patient's underlying disease.

Table 9: Summary of Adverse Reactions Reported in $\geq 5\%$ of the Lenalidomide Treated Patients in del 5q MDS Clinical Study

Body System Adverse Reaction ^a	10 mg Overall (N=148)	
Patients with at least one adverse reaction	148	(100)
Blood and Lymphatic System Disorders		
Thrombocytopenia	91	(61)
Neutropenia	87	(59)
Anemia	17	(11)
Leukopenia	12	(8)
Febrile Neutropenia	8	(5)
Skin and Subcutaneous Tissue Disorders		
Pruritus	62	(42)
Rash	53	(36)
Dry Skin	21	(14)
Contusion	12	(8)
Night Sweats	12	(8)
Sweating Increased	10	(7)
Ecchymosis	8	(5)
Erythema	8	(5)
Gastrointestinal Disorders		
Diarrhea	72	(49)
Constipation	35	(24)
Nausea	35	(24)
Abdominal Pain	18	(12)

Vomiting	15	(10)
Abdominal Pain Upper	12	(8)
Dry Mouth	10	(7)
Loose Stools	9	(6)
Respiratory, Thoracic and Mediastinal Disorders		
Nasopharyngitis	34	(23)
Cough	29	(20)
Dyspnea	25	(17)
Pharyngitis	23	(16)
Epistaxis	22	(15)
Dyspnea Exertional	10	(7)
Rhinitis	10	(7)
Bronchitis	9	(6)
General Disorders and Administration Site Conditions		
Fatigue	46	(31)
Pyrexia	31	(21)
Edema Peripheral	30	(20)
Asthenia	22	(15)
Edema	15	(10)
Pain	10	(7)
Rigors	9	(6)
Chest Pain	8	(5)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	32	(22)
Back Pain	31	(21)
Muscle Cramp	27	(18)
Pain in Limb	16	(11)
Myalgia	13	(9)
Peripheral Swelling	12	(8)
Nervous System Disorders		
Dizziness	29	(20)
Headache	29	(20)
Hypoesthesia	10	(7)
Dysgeusia	9	(6)
Peripheral Neuropathy	8	(5)
Infections and Infestations		
Upper Respiratory Tract Infection	22	(15)
Pneumonia	17	(11)
Urinary Tract Infection	16	(11)
Sinusitis	12	(8)
Cellulitis	8	(5)
Metabolism and Nutrition Disorders		
Hypokalemia	16	(11)
Anorexia	15	(10)
Hypomagnesemia	9	(6)
Investigations		
Alanine Aminotransferase Increased	12	(8)
Psychiatric Disorders		
Insomnia	15	(10)
Depression	8	(5)
Renal and Urinary Disorders		

Dysuria	10	(7)
Vascular Disorders		
Hypertension	9	(6)
Endocrine Disorders		
Acquired Hypothyroidism	10	(7)
Cardiac Disorders		
Palpitations	8	(5)

^a Body System and adverse reactions are coded using the MedDRA dictionary. Body System and adverse reactions are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an adverse reaction is counted only once under the applicable Body System/Adverse Reaction.

Table 10: Most Frequently Observed Grade 3 and 4 Adverse Reactions ¹ Regardless of Relationship to Study Drug Treatment in the del 5q MDS Clinical Study

Adverse Reactions ²	10 mg (N=148)
Patients with at least one Grade 3/4 AE	131 (89)
Neutropenia	79 (53)
Thrombocytopenia	74 (50)
Pneumonia	11 (7)
Rash	10 (7)
Anemia	9 (6)
Leukopenia	8 (5)
Fatigue	7 (5)
Dyspnea	7 (5)
Back Pain	7 (5)
Febrile Neutropenia	6 (4)
Nausea	6 (4)
Diarrhea	5 (3)
Pyrexia	5 (3)
Sepsis	4 (3)
Dizziness	4 (3)
Granulocytopenia	3 (2)
Chest Pain	3 (2)
Pulmonary Embolism	3 (2)
Respiratory Distress	3 (2)
Pruritus	3 (2)
Pancytopenia	3 (2)
Muscle Cramp	3 (2)
Respiratory Tract Infection	2 (1)
Upper Respiratory Tract Infection	2 (1)
Asthenia	2 (1)
Multi-organ Failure	2 (1)
Epistaxis	2 (1)
Hypoxia	2 (1)
Pleural Effusion	2 (1)
Pneumonitis	2 (1)

Pulmonary Hypertension	2 (1)
Vomiting	2 (1)
Sweating Increased	2 (1)
Arthralgia	2 (1)
Pain in Limb	2 (1)
Headache	2 (1)
Syncope	2 (1)

¹ Adverse reactions 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.

² Adverse reactions are coded using the MedDRA dictionary. A patient with multiple occurrences of an adverse reaction is counted only once in the adverse reaction category.

In other clinical studies of lenalidomide in MDS patients, the following serious adverse reactions (regardless of relationship to study drug treatment) not described in Table 9 or 10 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

Mantle Cell Lymphoma:

In the MCL trial, a total of 134 patients received at least 1 dose of lenalidomide. Their median age was 67 (range 43 to 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 11 summarizes the most frequently observed adverse reactions regardless of relationship to treatment with lenalidomide. Across the 134 patients treated in this study, median duration of treatment was 95 days (1 to 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 reactions, and 51 patients (38%) underwent at least one dose reduction due to adverse reactions. Twenty-six patients (19%) discontinued treatment due to adverse reactions.

Table 11: Incidence of Adverse Reactions (≥10%) or Grade 3/4 AE (in at least 2 patients) in Mantle Cell Lymphoma

Body System Adverse Reaction	All Adverse Reactions¹ (N=134) n (%)	Grade 3/4 Adverse Reactions² (N=134) n (%)
General disorders and administration site conditions		
Fatigue	45 (34)	9 (7)
Pyrexia ^{\$}	31 (23)	3 (2)
Edema peripheral	21 (16)	0
Asthenia ^{\$}	19 (14)	4 (3)
General physical health deterioration	3 (2)	2 (1)

Gastrointestinal disorders		
Diarrhea ^{\$}	42 (31)	8 (6)
Nausea ^{\$}	40 (30)	1 (<1)
Constipation	21 (16)	1 (<1)
Vomiting ^{\$}	16 (12)	1 (<1)
Abdominal pain ^{\$}	13 (10)	5 (4)
Musculoskeletal and connective tissue disorders		
Back pain	18 (13)	2 (1)
Muscle spasms	17 (13)	1 (<1)
Arthralgia	11 (8)	2 (1)
Muscular weakness ^{\$}	8 (6)	2 (1)
Respiratory, thoracic and mediastinal disorders		
Cough	38 (28)	1 (<1)
Dyspnea ^{\$}	24 (18)	8 (6)
Pleural Effusion	10 (7)	2 (1)
Hypoxia	3 (2)	2 (1)
Pulmonary embolism	3 (2)	2 (1)
Respiratory distress ^{\$}	2 (1)	2 (1)
Oropharyngeal pain	13 (10)	0
Infections and infestations		
Pneumonia ^{@ \$}	19 (14)	12 (9)
Upper respiratory tract infection	17 (13)	0
Cellulitis ^{\$}	3 (2)	2 (1)
Bacteremia ^{\$}	2 (1)	2 (1)
Staphylococcal sepsis ^{\$}	2 (1)	2 (1)
Urinary tract infection ^{\$}	5 (4)	2 (1)
Skin and subcutaneous tissue disorders		
Rash ⁺	30 (22)	2 (1)
Pruritus	23 (17)	1 (<1)
Blood and lymphatic system disorders		
Neutropenia	65 (49)	58 (43)
Thrombocytopenia ^{% \$}	48 (36)	37 (28)
Anemia ^{\$}	41 (31)	15 (11)
Leukopenia ^{\$}	20 (15)	9 (7)
Lymphopenia	10 (7)	5 (4)
Febrile neutropenia ^{\$}	8 (6)	8 (6)
Metabolism and nutrition disorders		
Decreased appetite	19 (14)	1 (<1)
Hypokalemia	17 (13)	3 (2)
Dehydration ^{\$}	10 (7)	4 (3)
Hypocalcemia	4 (3)	2 (1)
Hyponatremia	3 (2)	3 (2)
Renal and urinary disorders		
Renal failure ^{\$}	5 (4)	2 (1)
Vascular disorders		
Hypotension ^{@ \$}	9 (7)	4 (3)
Deep vein	5 (4)	5 (4)

thrombosis ^{\$}	3 (4)	3 (4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Tumor flare	13 (10)	0
Squamous cell carcinoma of skin ^{\$}	4 (3)	4 (3)
Investigations		
Weight decreased	17 (13)	0

¹-MCL trial AEs - All treatment emergent AEs with ≥10% of subjects.

²-MCL trial Grade 3/4 AEs - All treatment-emergent Grade 3/4 AEs in 2 or more subjects.

^{\$}-MCL trial Serious AEs - All treatment-emergent SAEs in 2 or more subjects.

@ - Adverse reactions where at least one resulted in a fatal outcome.

% - Adverse reactions where at least one was considered to be Life Threatening (if the outcome of the event was death, it is included with death cases).

- All adverse reactions under Body System of Infections except for rare infections of Public Health interest will be considered listed.

+ - All adverse reactions under HLT of Rash will be considered listed.

The following adverse reactions which have occurred in other indications including another MCL study and not described above have been reported (1% to 10%) in patients treated with lenalidomide monotherapy for mantle cell lymphoma.

Cardiac disorder: Cardiac failure

Ear and labyrinth disorders: Vertigo

General disorders and administration site conditions: Chills

Infections and infestations: Respiratory tract infection, sinusitis, nasopharyngitis, oral herpes

Musculoskeletal and connective tissue disorders: Pain in extremity

Nervous system disorders: Dysgeusia, headache, neuropathy peripheral, lethargy

Psychiatric disorders: Insomnia

Skin and subcutaneous tissue disorders: Dry skin, night sweats

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

Blood and lymphatic system disorders: Neutropenia

Cardiac disorder: Myocardial infarction (including acute MI), supraventricular tachycardia

Infections and infestations: *Clostridium difficile* colitis, sepsis

Neoplasms benign, malignant and unspecified (including cysts and polyps): Basal cell carcinoma

Respiratory, thoracic, and mediastinal disorders: Chronic obstructive pulmonary

disease, pulmonary embolism

6.2 Postmarketing Experience

The following adverse drug reactions have been identified from the worldwide post-marketing experience with lenalidomide capsules. 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 (5.8 to 5.11, and 5.13)*].

Endocrine disorders: Hypothyroidism, hyperthyroidism

Hepatobiliary disorders: Hepatic failure (including fatality), toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, mixed cytolytic/cholestatic hepatitis, transient abnormal liver laboratory tests

Immune system disorders: Angioedema, anaphylaxis, acute graft-versus-host disease (following allogeneic hematopoietic transplant), solid organ transplant rejection

Infections and infestations: Viral reactivation (such as hepatitis B virus and herpes zoster), progressive multifocal leukoencephalopathy (PML)

Neoplasms benign, malignant and unspecified (including cysts and polyps): Tumor lysis syndrome, tumor flare reaction

Respiratory, thoracic and mediastinal disorders: Pneumonitis

Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS)

7 DRUG INTERACTIONS

7.1 Digoxin

When digoxin was co-administered with multiple doses of lenalidomide capsules (10 mg/day) the digoxin C_{max} and AUC_{inf} were increased by 14%. Periodically monitor digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, during administration of lenalidomide capsules.

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 lenalidomide [see *Warnings and Precautions (5.4)*].

7.3 Warfarin

Co-administration of multiple doses of lenalidomide capsules (10 mg/day) with a single dose of warfarin (25 mg) had no effect on the pharmacokinetics of 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 lenalidomide capsules administration. It is not known whether there is an interaction between dexamethasone and warfarin. Close monitoring of PT and INR is recommended in patients with MM taking concomitant warfarin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in females exposed to lenalidomide capsules during pregnancy as well as female partners of male patients who are exposed to lenalidomide capsules. This registry is also used to understand the root cause for the pregnancy. Report any suspected fetal exposure to lenalidomide capsules to the FDA via the MedWatch program at 1-800-FDA-1088 and also to the REMS Call Center at 1-888-423-5436.

Risk Summary

Based on the mechanism of action [see *Clinical Pharmacology (12.1)*] and findings from animal studies [see *Data*], lenalidomide can cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy [see *Boxed Warning, Contraindications (4.1), and Use in Specific Populations (5.1)*].

Lenalidomide 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. Lenalidomide crossed the placenta after administration to pregnant rabbits and pregnant rats [see *Data*]. 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 risk 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. Report any suspected fetal exposure to lenalidomide capsules to the FDA via the MedWatch program at 1-800-FDA-1088 and also to the REMS Call Center at 1-888-423-5436.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

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.

Following daily oral administration of lenalidomide from Gestation Day 7 through Gestation Day 20 in pregnant rabbits, fetal plasma lenalidomide concentrations were approximately 20% to 40% of the maternal C_{max}. Following a single oral dose to pregnant rats, lenalidomide was detected in fetal plasma and tissues; concentrations of radioactivity in fetal tissues were generally lower than those in maternal tissues. These data indicated that lenalidomide crossed the placenta.

8.2 Lactation

Risk Summary

There is no information regarding the presence of lenalidomide in human milk, the effects of lenalidomide capsules on the breastfed child, or the effects of lenalidomide on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed children from lenalidomide capsules, advise women not to breastfeed during treatment with lenalidomide capsules.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Lenalidomide capsules can cause fetal harm when administered during pregnancy [see *Use in Specific Populations (8.1)*]. Verify the pregnancy status of females of reproductive potential prior to initiating lenalidomide capsules therapy and during therapy. Advise females of reproductive potential that they must avoid pregnancy 4 weeks before therapy, while taking lenalidomide capsules, during dose interruptions and for at least 4 weeks after completing therapy.

Females of reproductive potential must have 2 negative pregnancy tests before initiating lenalidomide capsules. The first test should be performed within 10 to 14 days, and the second test within 24 hours prior to prescribing lenalidomide capsules. 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. Lenalidomide treatment must be discontinued during this evaluation.

Contraception

Females

Females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 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 1 additional effective contraceptive method – male latex or synthetic condom, diaphragm, or cervical cap. Contraception must begin 4 weeks prior to initiating treatment with lenalidomide capsules, during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of lenalidomide 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.

Males

Lenalidomide is present in the semen of males who take lenalidomide capsules. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking lenalidomide capsules and for up to 4 weeks after discontinuing lenalidomide capsules, even if they have undergone a

successful vasectomy. Male patients taking lenalidomide capsules must not donate sperm and for up to 4 weeks after discontinuing lenalidomide capsules.

8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use

MM In Combination: 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 adverse reaction categories (eg, all adverse reactions, grade 3/4 adverse reactions, serious adverse reactions) was higher in older (> 75 years of age) than in younger (\leq 75 years of age) subjects. Grade 3 or 4 adverse reactions in the General Disorders and Administration Site Conditions body system 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 adverse reactions 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) body systems were also reported slightly, but consistently, more frequently (<5% difference), in older subjects than in younger subjects across all treatment arms. For other body systems (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 adverse reactions in older vs younger subjects across all treatment arms. Serious adverse reactions were generally reported at a higher frequency in the older subjects than in the younger subjects across all treatment arms.

MM 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 lenalidomide/dexamethasone and placebo/dexamethasone groups. Of the 353 patients who received lenalidomide/dexamethasone, 46% were age 65 and over. In both studies, patients > 65 years of age were more likely than patients \leq 65 years of age to experience DVT, pulmonary embolism, atrial fibrillation, and renal failure following use of lenalidomide capsules. No differences in efficacy were observed between patients over 65 years of age and younger patients.

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 reactions (100%) was the same in patients over 65 years of age as in younger patients, the frequency of serious adverse reactions 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 reactions 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.

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 reactions 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 reactions was also similar in these 2 patient groups (79% vs. 78%, respectively). The frequency of serious adverse reactions 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 Renal Impairment

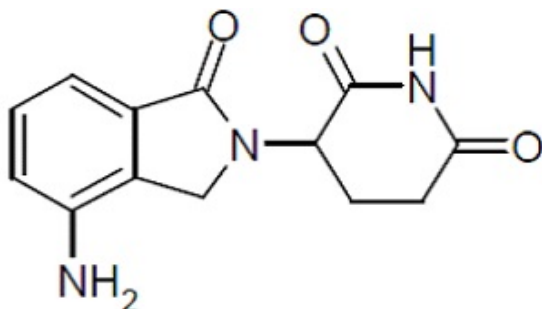
Adjust the starting dose of lenalidomide capsules based on the creatinine clearance value and for patients on dialysis [see *Dosage and Administration (2.6)*].

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

Lenalidomide, 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 C₁₃H₁₃N₃O₃, and the gram molecular weight is 259.3.

Lenalidomide is a cream to light yellow color 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.

Lenalidomide is available in 2.5 mg and 20 mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: anhydrous lactose. The capsule shell ingredients common for both strengths are gelatin and titanium dioxide. Additionally, the 20 mg capsule contains FD&C Blue #1, FD&C Yellow #6, and iron oxide yellow. Each capsule is printed with black ink, which includes black iron oxide, potassium hydroxide, propylene glycol, shellac, and strong ammonia solution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lenalidomide is an analogue of thalidomide with immunomodulatory, antiangiogenic, and antineoplastic properties. Cellular activities of lenalidomide are mediated through its target cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex. *In vitro*, in the presence of drug, substrate proteins (including Aiolos, Ikaros, and CK1 α) are targeted for ubiquitination and subsequent degradation leading to direct cytotoxic and immunomodulatory effects. Lenalidomide inhibits proliferation and induces apoptosis of certain hematopoietic tumor cells including MM, 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 MM. Immunomodulatory properties of lenalidomide include increased number and activation of T cells and natural killer (NK) cells leading to direct and enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) via increased secretion of interleukin-2 and interferon-gamma, increased numbers of NKT cells, and inhibition of pro-inflammatory cytokines (e.g., TNF- α and IL-6) by monocytes. In MM cells, the combination of lenalidomide and dexamethasone synergizes the inhibition of cell proliferation and the induction of apoptosis.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of lenalidomide on the QTc interval was evaluated in 60 healthy male subjects in a thorough QT study. At a dose two times the maximum recommended dose, lenalidomide did not prolong the QTc interval. The largest upper bound of the two-sided 90% CI for the mean differences between lenalidomide and placebo was below 10 ms.

12.3 Pharmacokinetics

Absorption

Following single and multiple doses of lenalidomide capsules 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 doses of lenalidomide at the recommended dosage does not result in drug accumulation.

Administration of a single 25 mg dose of lenalidomide capsules 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 lenalidomide capsules, the drug was administered without regard to food intake. Lenalidomide capsules can be administered with or without food.

The oral absorption rate of lenalidomide in patients with MCL is similar to that observed in patients with MM or MDS.

Distribution

In vitro [¹⁴C]-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 lenalidomide 25 mg daily.

Elimination

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

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.

Excretion

Elimination is primarily renal. Following a single oral administration of [¹⁴C]-lenalidomide 25 mg to healthy subjects, approximately 90% and 4% of the radioactive dose was eliminated within ten days in urine and feces, respectively. Approximately 82% of the radioactive dose was excreted as lenalidomide in the urine within 24 hours. Hydroxy-lenalidomide and N-acetyl-lenalidomide represented 4.6% and 1.8% of the excreted dose, respectively. The renal clearance of lenalidomide exceeds the glomerular filtration rate.

Specific Populations

Renal Impairment: Eight subjects with mild renal impairment (creatinine clearance (CLcr) 50 to 79 mL/min calculated using Cockcroft-Gault), 9 subjects with moderate renal impairment (CLcr 30 to 49 mL/min), 4 subjects with severe renal impairment (CLcr < 30 mL/min), and 6 patients with end stage renal disease (ESRD) requiring dialysis were administered a single 25 mg dose of lenalidomide capsules. Three healthy subjects of similar age with normal renal function (CLcr > 80 mL/min) were also administered a single 25 mg dose of lenalidomide capsules. As CLcr decreased, half-life increased and drug clearance decreased linearly. Patients with moderate and severe 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) had 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.

Adjust the starting dose of lenalidomide capsules in patients with renal impairment based on the CLcr value [see *Dosage and Administration (2.6)*].

Hepatic Impairment: Mild hepatic impairment (defined as total bilirubin > 1 to 1.5 times upper limit normal (ULN) or any aspartate transaminase greater than ULN) did not influence the disposition of lenalidomide. No pharmacokinetic data is available for patients with moderate to severe hepatic impairment.

Other Intrinsic Factors: Age (39 to 85 years), body weight (33 to 135 kg), sex, race, and type of hematological malignancies (MM, MDS or MCL) did not have a clinically relevant effect on lenalidomide clearance in adult patients.

Drug Interactions

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

Co-administration of lenalidomide capsules (25 mg) after multiple doses of a P-gp inhibitor such as quinidine (600 mg twice daily) did not significantly increase the C_{max} or AUC of lenalidomide.

Co-administration of the P-gp inhibitor and substrate temsirolimus (25 mg), with lenalidomide capsules (25 mg) did not significantly alter the pharmacokinetics of lenalidomide, temsirolimus, or sirolimus (metabolite of temsirolimus).

In vitro studies demonstrated that lenalidomide is a substrate of P-glycoprotein (P-gp). Lenalidomide 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), 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 P-gp, bile salt export pump (BSEP), BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2. Lenalidomide does not inhibit or induce CYP450 isoenzymes. Also, 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.

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 MM:

A randomized multicenter, open-label, 3-arm trial of 1,623 patients, was conducted to compare the efficacy and safety of lenalidomide and low-dose dexamethasone (Rd) given for 2 different durations of time to that of melphalan, prednisone and thalidomide (MPT) in newly diagnosed MM 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 lenalidomide 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% \geq Grade 3.

The primary efficacy endpoint, progression-free survival (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 to 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 13: Overview of Efficacy Results - Study MM-020 (Intent-to-treat Population)

	Rd Continuous (N=535)	Rd18 (N=541)	MPT (N=547)
PFS – IRAC (months)^g			
Number of PFS events	278 (52)	348 (64.3)	334 (61.1)
Median ^a PFS time, months (95% CI) ^b	25.5 (20.7, 29.4)	20.7 (19.4, 22)	21.2 (19.3, 23.2)
HR [95% CI] ^c ; p-value ^d			
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)		
Overall Survival (months)^h			
Number of Death events	208 (38.9)	228 (42.1)	261 (47.7)
Median ^a OS time, months (95% CI) ^b	58.9 (56, NE) ^f	56.7 (50.1, NE)	48.5 (44.2, 52)
HR [95% CI] ^c			
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)		
Response Rate^e – IRAC, n (%)^g			
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.

^a The median is based on the Kaplan-Meier estimate.

^b The 95% Confidence Interval (CI) about the median.

^c Based on Cox proportional hazards model comparing the hazard functions associated with the indicated treatment arms.

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

^e Best assessment of response during the treatment phase of the study.

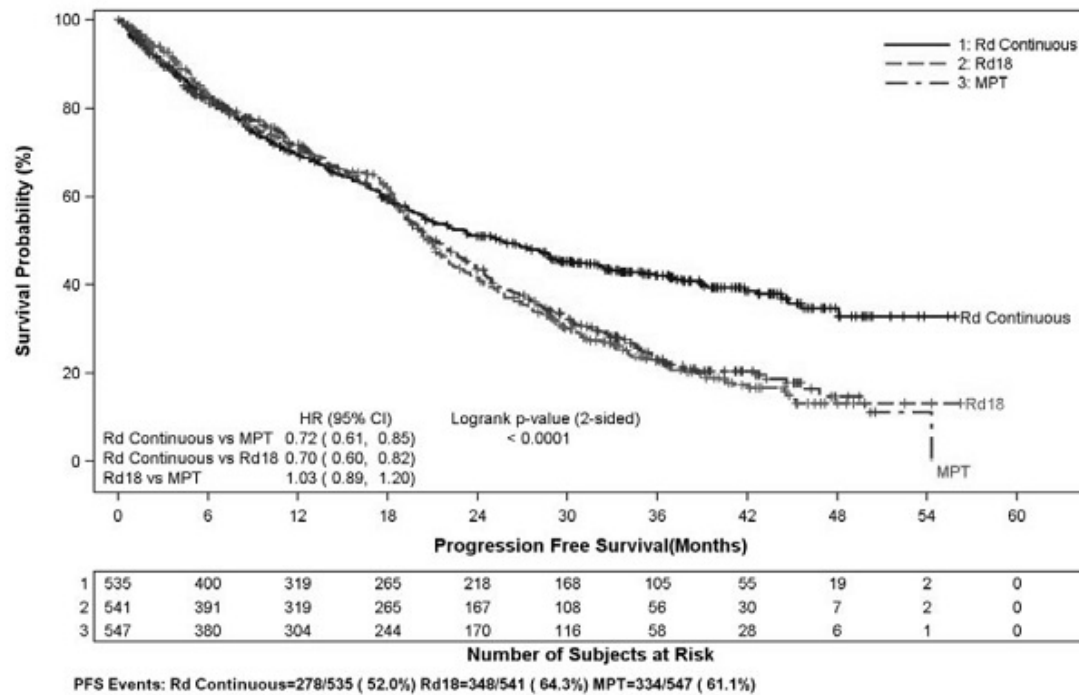
^f Including patients with no response assessment data or whose only assessment was "response not evaluable."

^g Data cutoff date = 24 May 2013.

^h Data cutoff date = 3 March 2014.

Kaplan-Meier Curves of Progression-free Survival Based on IRAC Assessment (ITT MM Population) Between Arms Rd Continuous, Rd18 and MPT

Cutoff date: 24 May 2013

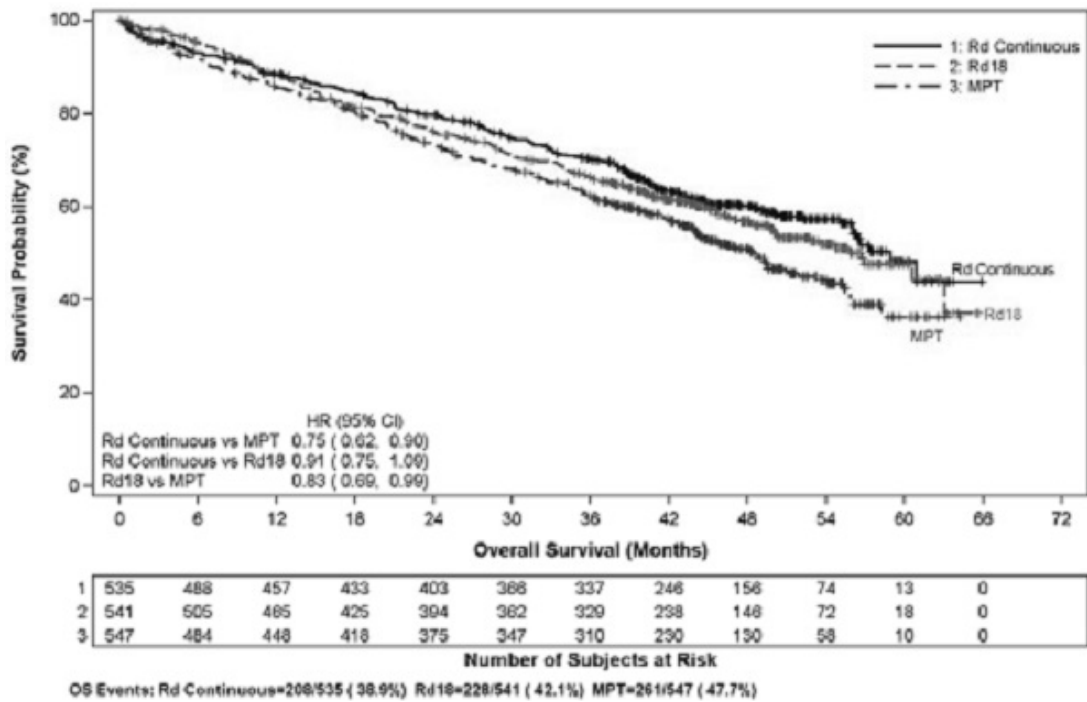


CI = confidence interval; d = low-dose dexamethasone; HR = hazard ratio; IRAC = Independent Response Adjudication Committee; M = melphalan; P = prednisone; R = lenalidomide; Rd Continuous = Rd given until documentation of progressive disease; Rd18 = Rd given for ≤ 18 cycles; T = thalidomide.

Kaplan-Meier Curves of Overall Survival (ITT MM 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 MM After At Least One Prior Therapy

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

In both studies, patients in the lenalidomide/dexamethasone group took 25 mg of lenalidomide 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 16 summarizes the baseline patient and disease characteristics in the two studies. In both studies, baseline demographic and disease-related characteristics were comparable between the lenalidomide/dexamethasone and placebo/dexamethasone groups.

Table 16: Baseline Demographic and Disease-Related Characteristics - MM Studies 1 and 2

	Study 1		Study 2	
	Lenalidomide/Dex N=177	Placebo/Dex N=176	Lenalidomide/Dex N=176	Placebo/Dex N=175
Patient Characteristics				
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%)
Disease Characteristics				
Multiple Myeloma Stage (Durie-Salmon)				
I	3%	3%	6%	5%
II	32%	31%	28%	33%
III	64%	66%	65%	63%
β2-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%)
Number of Prior Therapies				
1	38%	38%	32%	33%
≥ 2	62%	62%	68%	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.

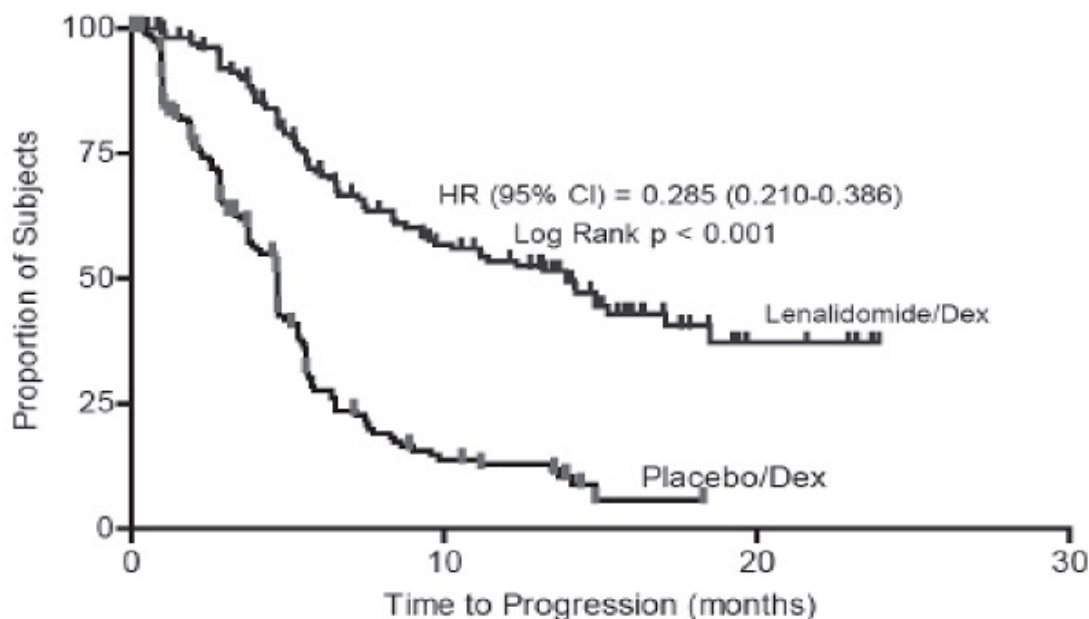
Preplanned interim analyses of both studies showed that the combination of lenalidomide/dexamethasone was significantly superior to dexamethasone alone for TTP. The studies were unblinded to allow patients in the placebo/dexamethasone group to receive treatment with the lenalidomide/dexamethasone combination. 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

lenalidomide/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 to 1.03). In study 2, the median survival time was 37.5 months (95% CI: 29.9, 46.6) in lenalidomide/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 to 1.14).

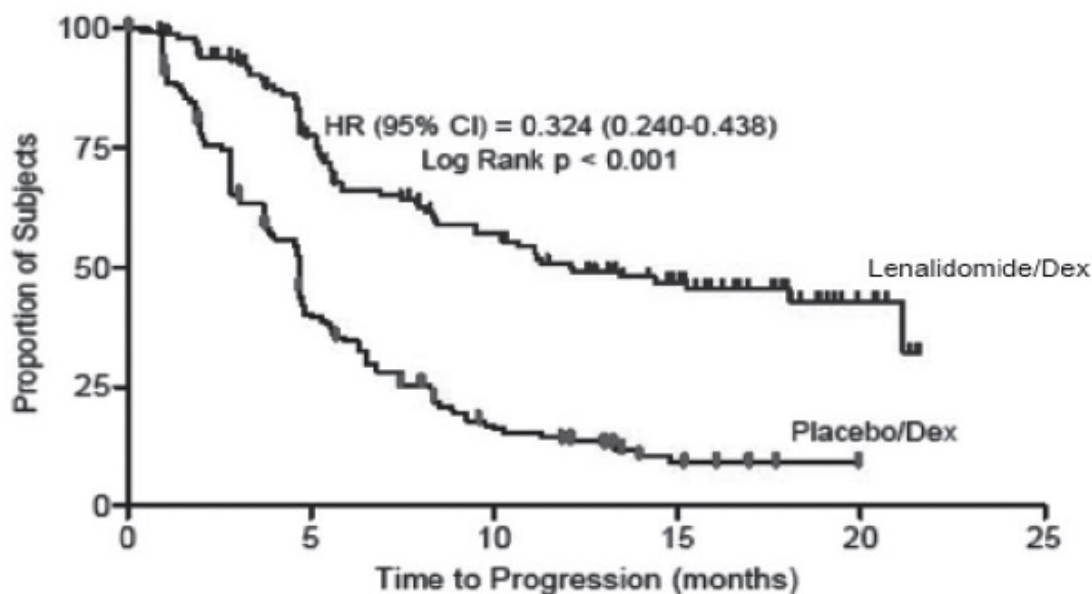
Table 17: TTP Results in MM Study 1 and Study 2

	Study 1		Study 2	
	Lenalidomide/Dex N=177	Placebo/Dex N=176	Lenalidomide/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]	

Kaplan-Meier Estimate of Time to Progression — MM Study 1



Kaplan-Meier Estimate of Time to Progression — MM Study 2



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

The efficacy and safety of lenalidomide capsules were evaluated in patients with transfusion-dependent anemia in low- or intermediate-1-risk MDS with a 5q (q31 to 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 [see *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) $\geq 500/\text{mm}^3$, platelet counts $\geq 50,000/\text{mm}^3$, serum creatinine ≤ 2.5 mg/dL, serum SGOT/AST or SGPT/ALT $\leq 3 \times$ upper limit of normal (ULN), and serum direct bilirubin ≤ 2 mg/dL. Granulocyte colony-stimulating factor was permitted for patients who developed neutropenia or fever in association with neutropenia. Baseline patient and disease-related characteristics are summarized in Table 18.

Table 18: Baseline Demographic and Disease-Related Characteristics in the MDS Study

	Overall (N=148)	
Age (years)		
Median		71
Min, Max		37, 95
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)
Other cytogenetic abnormalities	37	(25.2)
IPSS Score ^a	n	(%)
Low (0)	55	(37.2)
Intermediate-1 (0.5 to 1.0)	65	(43.9)
Intermediate-2 (1.5 to 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)
RARS	16	(10.8)
RAEB	30	(20.3)
CMML	3	(2)

^a IPSS Risk Category: Low (combined score = 0), Intermediate-1 (combined score = 0.5 to 1), 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 lenalidomide capsules 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 to 253 days), and the median duration of the first dose interruption was 22 days (mean, 28.5 days; range, 2 to 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 to 205 days) and the median duration of the second dose interruption was 21 days (mean, 26 days; range, 2 to 148 days).

14.3 Mantle Cell Lymphoma

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

The trial included patients who were at least 18 years of age with biopsy-proven MCL with measurable disease by CT scan. Patients were required to have received prior

treatment with an anthracycline or mitoxantrone, cyclophosphamide, rituximab, and bortezomib, alone or in combination. Patients were required to have documented refractory disease (defined as without any response of PR or better during treatment with bortezomib or a bortezomib-containing regimen), or relapsed disease (defined as progression within one year after treatment with bortezomib or a bortezomib-containing regimen). At enrollment patients were to have an absolute neutrophil counts (ANC) $\geq 1500/\text{mm}^3$, platelet counts $\geq 60,000/\text{mm}^3$, serum SGOT/AST or SGPT/ALT $\leq 3\times$ upper limit of normal (ULN) unless there was documented evidence of liver involvement by lymphoma, serum total bilirubin $\leq 1.5 \times$ ULN except in cases of Gilbert's syndrome or documented liver involvement by lymphoma, and calculated creatinine clearance (Cockcroft-Gault formula) ≥ 30 mL/min.

The median age was 67 years (43 to 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 19: Baseline Disease-related Characteristics and Prior Anti-Lymphoma Therapy in Mantle Cell Lymphoma Trial

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

Prior Autologous Bone Marrow or Stem Cell Transplant, n (%)	39 (29)
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^a ECOG = Eastern Cooperative Oncology Group.

^b MIPI = MCL International Prognostic Index.

^c High tumor burden is defined as at least one lesion that is ≥ 5 cm in diameter or 3 lesions that are ≥ 3 cm in diameter.

^d Bulky disease is defined as at least one lesion that is ≥ 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 20. The median time to response was 2.2 months (range 1.8 to 13 months).

Table 20: 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

Lenalidomide capsules are available as follows:

2.5 mg – Each size 4 capsule with white cap and body printed with “NAT” on cap and “2.5mg” on body in black ink contains 2.5 mg of lenalidomide.

2.5 mg bottles of 28 (NDC 0480-1241-28)

2.5 mg bottles of 100 (NDC 0480-1241-01)

20 mg – Each size 2 capsule with green cap and blue body printed with “NAT” on cap and “20 mg” on body in black ink contains 20 mg of lenalidomide.

20 mg bottles of 21 (NDC 0480-1245-21)
20 mg bottles of 100 (NDC 0480-1245-01)

16.2 Storage

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

16.3 Handling and Disposal

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

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

Dispense no more than a 28-day supply.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved Patient labeling (Medication Guide)

Embryo-Fetal Toxicity

Advise patients that lenalidomide capsules are contraindicated in pregnancy [see *Boxed Warning and Contraindications (4.1)*]. Lenalidomide is a thalidomide analogue 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 lenalidomide capsules and for at least 4 weeks after completing therapy.
- Initiate lenalidomide capsules 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 2 different forms of contraception including at least 1 highly effective form, simultaneously during lenalidomide capsules therapy, during dose interruption and for 4 weeks after she has completely finished taking lenalidomide capsules. 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 lenalidomide capsules and contact her healthcare provider 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 healthcare provider is not available, she should call the REMS Call Center at 1-888-423-5436 [see *Warnings and Precautions (5.1) and Use in Specific Populations (8.3)*].
- Advise males to always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking lenalidomide capsules and for up to 4 weeks after discontinuing lenalidomide capsules, even if they have undergone a successful vasectomy.
- Advise male patients taking lenalidomide capsules that they must not donate sperm and for up to 4 weeks after discontinuation of lenalidomide capsules [see *Warnings and Precautions (5.1) and Use in Specific Populations (8.3)*].
- All patients must be instructed to not donate blood while taking lenalidomide

capsules, during dose interruptions and for 4 weeks following discontinuation of lenalidomide capsules [see *Warnings and Precautions (5.1)*].

Lenalidomide REMS program

Because of the risk of embryo-fetal toxicity, lenalidomide capsules are only available through a restricted program called the Lenalidomide REMS program [see *Warnings and Precautions (5.2)*].

- Patients must sign a Patient-Physician agreement form and comply with the requirements to receive lenalidomide capsules. 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 (8.3)*].
- Lenalidomide capsules are available only from pharmacies that are certified in Lenalidomide REMS program. Provide patients with the telephone number and website for information on how to obtain the product.

Pregnancy Exposure Registry

Inform females there is a Pregnancy Exposure Registry that monitors pregnancy outcomes in females exposed to lenalidomide capsules during pregnancy and that they can contact the Pregnancy Exposure Registry by calling 1-888-423-5436 [see *Use in Specific Populations (8.1)*].

Hematologic Toxicity

Inform patients that lenalidomide capsules are associated with significant neutropenia and thrombocytopenia [see *Boxed Warning 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 Warning and Warnings and Precautions (5.4)*].

Increased Mortality in Patients with CLL

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

Second Primary Malignancies

Inform patients of the potential risk of developing second primary malignancies during treatment with lenalidomide capsules [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 (5.8)*].

Severe Cutaneous Reactions

Inform patients of the potential risk for severe skin reactions such as SJS, TEN, and DRESS and report any signs and symptoms associated with these reactions to their healthcare provider for evaluation. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive lenalidomide capsules [see *Warnings and Precautions (5.9)*].

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 (5.10)].

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 (5.11)].*

Early Mortality in Patients with MCL

Inform patients with MCL of the potential for early death [see *Warnings and Precautions (5.14)].*

Hypersensitivity

Inform patients of the potential for severe hypersensitivity reactions such as angioedema and anaphylaxis to lenalidomide capsules. Instruct patients to contact their healthcare provider right away for signs and symptoms of these reactions. Advise patients to seek emergency medical attention for signs or symptoms of severe hypersensitivity reactions [see *Warnings and Precautions (5.15)].*

Dosing Instructions

Inform patients how to take lenalidomide capsules [see *Dosage and Administration (2)]*

- Lenalidomide capsules should be taken once daily at about the same time each day,
- Lenalidomide capsules may be taken either with or without food.
- The capsules should not be opened, broken, or chewed. Lenalidomide capsules should be swallowed whole with water.
- Instruct patients that if they miss a dose of lenalidomide capsules, 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 lenalidomide capsules at the usual time. Warn patients to not take 2 doses to make up for the one that they missed.

Manufactured In India By:

Natco Pharma Limited

Kothur - 509 228, India

Manufactured For:

Teva Pharmaceuticals

Parsippany, NJ 07054

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MEDICATION GUIDE

LENALIDOMIDE (len" a lid' oh mide) Capsules

What is the most important information I should know about lenalidomide capsules?

Before you begin taking lenalidomide capsules, you must read and agree to all of the instructions in the Lenalidomide REMS program. Before prescribing lenalidomide capsules, your healthcare provider will explain the Lenalidomide REMS program to you and have you sign the Patient-Physician Agreement Form.

Lenalidomide capsules 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 lenalidomide capsules.

Lenalidomide is similar to the medicine thalidomide. We know thalidomide can

cause severe

life-threatening birth defects. Lenalidomide capsules have not been tested in pregnant females. Lenalidomide capsules have harmed unborn animals in animal testing.

Females must not get pregnant:

- For at least 4 weeks before starting lenalidomide capsules
- While taking lenalidomide capsules
- During any breaks (interruptions) in your treatment with lenalidomide capsules
- For at least 4 weeks after stopping lenalidomide capsules

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 two acceptable forms of birth control at the same time, for at least 4 weeks before, while taking, during any breaks (interruptions) in your treatment, and for at least 4 weeks after stopping lenalidomide capsules.
- Talk with your healthcare provider to find out about options for acceptable forms of birth control that you may use to prevent pregnancy before, during, and after treatment with lenalidomide capsules.
- If you had unprotected sex or if you think your birth control has failed, stop taking lenalidomide capsules immediately and call your healthcare provider right away.

If you become pregnant while taking lenalidomide capsules, stop taking it right away and call your healthcare provider.

If your healthcare provider is not available, you can call the REMS Call Center at 1-888-423-5436. Healthcare providers and patients should report all cases of pregnancy to:

- FDA MedWatch at 1-800-FDA-1088, and
- The Lenalidomide REMS program at 1-888-423-5436

There is a pregnancy exposure registry that monitors the outcomes of females who take lenalidomide capsules during pregnancy, or if their male partner takes lenalidomide capsules and they are exposed during pregnancy. You can enroll in this registry by calling the Lenalidomide REMS program at the phone number listed above.

Lenalidomide can pass into human semen:

- Males, including those who have had a vasectomy, must always use a latex or synthetic condom during any sexual contact with a pregnant female or a female that can become pregnant while taking lenalidomide capsules, during any breaks (interruptions) in your treatment with lenalidomide capsules, and for up to 4 weeks after stopping lenalidomide capsules.
- 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 lenalidomide capsules, during any breaks (interruptions) in your treatment, and for up to 4 weeks after stopping lenalidomide capsules. If a female becomes pregnant with your sperm, the baby may be exposed to lenalidomide 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).** Lenalidomide capsules cause 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 lenalidomide capsules, and then at least monthly. Tell your healthcare provider if you develop any bleeding or bruising, during

treatment with lenalidomide capsules.

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

Before taking lenalidomide capsules, tell your healthcare provider:

- If you have had a blood clot in the past
- If you have high blood pressure, smoke, or if you have been told 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 lenalidomide capsules:

- **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 are lenalidomide capsules?

Lenalidomide capsules are a prescription medicine, used to treat adults with:

- multiple myeloma (MM)
 - in combination with the medicine dexamethasone
- a condition called myelodysplastic syndromes (MDS). Lenalidomide capsules are 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.
- mantle cell lymphoma (MCL) when the disease comes back or becomes worse after treatment with 2 prior medicines, one of which included bortezomib. MCL is a cancer of a type of white blood cell called lymphocytes that are in the lymph nodes.

Lenalidomide capsules 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 lenalidomide capsules are safe and effective in children.

Who should not take lenalidomide capsules?

Do not take lenalidomide capsules if you:

- **are pregnant, plan to become pregnant, or become pregnant during treatment with lenalidomide capsules. See “What is the most important information I should know about lenalidomide capsules?”**
- are allergic to lenalidomide or any of the ingredients in lenalidomide capsules. See the end of this Medication Guide for a complete list of ingredients in lenalidomide capsules.

What should I tell my healthcare provider before taking lenalidomide capsules?

Before you take lenalidomide capsules, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems
- have kidney problems or receive kidney dialysis treatment
- have thyroid problems

- have had a serious skin rash with thalidomide treatment. You should not take lenalidomide capsules.
- are lactose intolerant. Lenalidomide capsules contain lactose.
- are breastfeeding. Do not breastfeed during treatment with lenalidomide capsules. It is not known if lenalidomide 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. Lenalidomide capsules and other medicines may affect each other, causing serious side effects. Talk with your healthcare provider before taking any new medicines. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist.

How should I take lenalidomide capsules?

- Take lenalidomide capsules exactly as prescribed and follow all the instructions of the Lenalidomide REMS program
- Swallow lenalidomide capsules whole with water 1 time a day. **Do not open, break, or chew your capsules.**
- **Lenalidomide capsules may be taken with or without food.**
- Take lenalidomide capsules at about the same time each day.
- Do not open or break lenalidomide capsules or handle them any more than needed.
 - If powder from the lenalidomide capsule comes in contact with your skin, wash the skin right away with soap and water.
 - If powder from the lenalidomide capsule comes in contact with the inside of your eyes, nose, or mouth, flush well with water.
- If you miss a dose of lenalidomide capsules 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 lenalidomide, call your healthcare provider right away.

What should I avoid while taking lenalidomide capsules?

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

What are the possible side effects of lenalidomide capsules?

Lenalidomide capsules can cause serious side effects, including:

- See “What is the most important information I should know about lenalidomide capsules?”
- **Increased risk of death in people who have chronic lymphocytic leukemia (CLL).** People with CLL who take lenalidomide capsules have an increased risk of death compared with people who take the medicine chlorambucil. Lenalidomide capsules 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 lenalidomide capsules if you have CLL unless you are participating in a controlled clinical trial.
- **Risk of new cancers (malignancies).** An increase in new (second) cancers has

happened in patients who received lenalidomide capsules and melphalan, or a blood stem cell transplant, including certain blood cancers, such as acute myelogenous leukemia (AML), and myelodysplastic syndrome (MDS) and certain other types of cancers of the skin and other organs. Talk with your healthcare provider about your risk of developing new cancers if you take lenalidomide capsules. Your healthcare provider will check you for new cancers during your treatment with lenalidomide capsules.

- **Severe liver problems, including liver failure and death.** Your healthcare provider should do blood tests to check your liver function during your treatment with lenalidomide capsules. 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
- **Severe skin reactions and severe allergic reactions** can happen with lenalidomide capsules and may cause death.

Call your healthcare provider right away if you develop any of the following signs or symptoms during treatment with lenalidomide capsules:

- a red, itchy, skin rash
- peeling of your skin or blisters
- severe itching
- fever

Get emergency medical help right away if you develop any of the following signs or symptoms during treatment with lenalidomide capsules:

- swelling of your lips, mouth, tongue, or throat
 - trouble breathing or swallowing
 - raised red areas on your skin (hives)
 - a very fast heartbeat
 - you feel dizzy or faint
- **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)** can happen with lenalidomide capsules and may cause death. Tell your healthcare provider if you get any of these symptoms of tumor flare reaction during treatment with lenalidomide capsules: tender swollen lymph nodes, low grade fever, pain, or rash.

Your healthcare provider may tell you to decrease your dose, temporarily stop or permanently stop taking lenalidomide capsules if you develop certain serious side effects during treatment with lenalidomide capsules.

- **Thyroid problems.** Your healthcare provider may check your thyroid function before you start taking lenalidomide capsules and during treatment with lenalidomide capsules.
- **Risk of Early Death in MCL.** In people who have Mantle Cell Lymphoma (MCL), there may be a risk of dying sooner (early death) when taking lenalidomide capsules. Talk with your healthcare provider about any concerns and possible risk factors.

The most common side effects of lenalidomide capsules include:

- diarrhea
- swelling of your arms, hands, legs, feet and skin
- upper respiratory tract infection or bronchitis
- inflammation of the

- rash
- nausea
- constipation
- tiredness or weakness
- fever
- itching
- sleep problems (insomnia)
- headache
- muscle cramps or spasms
- shortness of breath
- cough, sore throat, and other symptoms of a cold
- inflammation of the stomach and intestine ("stomach flu")
- nose bleed
- shaking or trembling (tremor)
- joint aches
- pain in your back or stomach-area (abdomen)

These are not all the possible side effects of lenalidomide capsules. Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store lenalidomide capsules?

- Store lenalidomide capsules at room temperature between 68°F to 77°F (20°C to 25°C).
- Return any unused lenalidomide capsules to Teva or your healthcare provider.

Keep lenalidomide capsules and all medicines out of the reach of children.

General information about the safe and effective use of lenalidomide capsules.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not take lenalidomide capsules for conditions for which they were not prescribed. Do not give lenalidomide capsules 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 lenalidomide capsules that is written for health professionals.

What are the ingredients in lenalidomide capsules?

Active ingredient: lenalidomide

Inactive ingredients: anhydrous lactose. The capsule shell ingredients common for both strengths are gelatin and titanium dioxide. Additionally, the 20 mg capsule contains FD&C Blue #1, FD&C Yellow #6 and iron oxide yellow. Each capsule is printed with black ink, which includes black iron oxide, potassium hydroxide, propylene glycol, shellac, and strong ammonia solution.

Manufactured In India By: **Natco Pharma Limited**, Kothur - 509 228, India

Manufactured For: **Teva Pharmaceuticals**, Parsippany, NJ 07054

For more information, call 1-888-838-2872 or go to www.lenalidomiderems.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration.
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PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 0480-1241-28 Rx only

Lenalidomide Capsules
2.5 mg

WARNING: POTENTIAL FOR HUMAN BIRTH DEFECTS

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

28 Capsules

Each capsule contains:
Lenalidomide 2.5 mg
Store at 20°C to 25°C
(68°F to 77°F); excursions
permitted to 15°C to 30°C
(59°F to 86°F) [see USP
Controlled Room Temperature].
See prescribing information
for dosing and administration.

NDC 0480-1241-28 Rx only

**Lenalidomide
Capsules**
2.5 mg

**WARNING: POTENTIAL FOR
HUMAN BIRTH DEFECTS**


PHARMACIST: Dispense the
accompanying Medication Guide
to each patient.

28 Capsules


Manufactured In India By:
Natco Pharma Limited
Kothur - 509 228, India
Manufactured For:
Teva Pharmaceuticals
Parsippany, NJ 07054
M.L.: 164/MN/AP/95/F/R Iss. 7/2021

40100169

Serialization Coding Area



N 3 0 4 8 0 - 1 2 4 1 - 2 8 1



PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 0480-1245-21 Rx only

Lenalidomide Capsules
20 mg

WARNING: POTENTIAL FOR HUMAN BIRTH DEFECTS

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

21 Capsules

Each capsule contains:
Lenalidomide 20 mg
Store at 20°C to 25°C
(68°F to 77°F); excursions
permitted to 15°C to 30°C
(59°F to 86°F) [see USP
Controlled Room Temperature].
See prescribing information
for dosing and administration.

NDC 0480-1245-21 Rx only

**Lenalidomide
Capsules**
20 mg

**WARNING: POTENTIAL FOR
HUMAN BIRTH DEFECTS**

PHARMACIST: Dispense the
accompanying Medication Guide
to each patient.

21 Capsules


Manufactured In India By:
Natco Pharma Limited
Kothur - 509 228, India
Manufactured For:
Teva Pharmaceuticals
Parsippany, NJ 07054
M.L.: 164/MN/AP/95/F/R Iss. 7/2021

40100177

Serialization Coding Area



N 3 0 4 8 0 - 1 2 4 5 - 2 1 0



LENALIDOMIDE

lenalidomide capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0480-1241
Route of Administration	ORAL		
Active Ingredient/Active Moiety			
Ingredient Name	Basis of Strength	Strength	
LENALIDOMIDE (UNII: F0P408N6V4) (LENALIDOMIDE - UNII:F0P408N6V4)	LENALIDOMIDE	2.5 mg	

Inactive Ingredients				
Ingredient Name			Strength	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)				
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)				
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)				
FERROSFERRIC OXIDE (UNII: XM0M87F357)				
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)				
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)				
SHELLAC (UNII: 46N107B71O)				
AMMONIA (UNII: 5138Q19F1X)				
Product Characteristics				
Color	white	Score	no score	
Shape	CAPSULE	Size	14mm	
Flavor		Imprint Code	NAT;2;5mg	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0480-1241-28	28 in 1 BOTTLE; Type 0: Not a Combination Product	03/08/2023	
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
ANDA	ANDA201452	03/08/2023		

LENALIDOMIDE				
lenalidomide capsule				
Product Information				
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0480-1245	
Route of Administration	ORAL			
Active Ingredient/Active Moiety				
Ingredient Name		Basis of Strength	Strength	
LENALIDOMIDE (UNII: F0P408N6V4) (LENALIDOMIDE - UNII:F0P408N6V4)		LENALIDOMIDE	20 mg	
Inactive Ingredients				
Ingredient Name			Strength	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)				
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)				
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)				
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)				
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)				
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)				

FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SHELLAC (UNII: 46N107B71O)	
AMMONIA (UNII: 5138Q19F1X)	

Product Characteristics

Color	green, blue	Score	no score
Shape	CAPSULE	Size	18mm
Flavor		Imprint Code	NAT;20mg
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0480-1245-21	21 in 1 BOTTLE; Type 0: Not a Combination Product	03/08/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201452	03/08/2023	

Labeler - Teva Pharmaceuticals, Inc. (022629579)

Revised: 5/2022

Teva Pharmaceuticals, Inc.