Lidamid (Lenalidomide Capsules 5 mg, 10 mg, 15 mg & 25 mg), for oral use

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 potentia , 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)]*.

Hemato ogic 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 patients with multiple myeloma (MM).

1.2 Myelodysplastic Syndromes

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

1.3 Mantle Cell Lymphoma

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

1.4 Limitations of Use

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 (5.4)].

2 DOSAGE AND ADMINISTRATION

Lenalidomide capsules should be taken orally at about the same time each day, either with or without food. Lenalidomide capsules should be swallowed whole with water. The capsules should not be opened, broken, or chewed.

2.1 Multiple Myeloma

Lenalidomide Capsules Combination Therapy

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

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 to <30,000/mcL Return to ≥30,000/mcL	Interrupt lenalidomide treatment, follow CBC weekly Resume lenalidomide at next lower dose. Do not dose below 2.5 mg daily
For each subsequent drop <30,000/mcL Return to ≥30,000/mcL	Interrupt lenalidomide treatment Resume lenalidomide 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 to <1000/mcL Return to ≥1,000/mcL and neutropenia is the only toxicity	Interrupt lenalidomide treatment, follow CBC weekly Resume lenalidomide at 25 mg daily or initial starting dose
Return to ≥1,000/mcL and if other toxicity	Resume lenalidomide at next lower dose. Do not dose below 2.5 mg daily
For each subsequent drop <1,000/mcL Return to ≥1,000/mcL	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose. Do not dose below 2.5 mg daily

Dose Adjustments for Hematologic Toxicities During MM Treatment

Dose modification guidelines, as summarized in Table 2 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 2: Dose Adjustments for Hematologic Toxicities for MM
Platelet counts
Thrombocytopenia in MM

When Platelets	Recommended Course
Fall to <30,000/mcL Return to ≥30,000/mcL	Interrupt lenalidomide treatment, follow CBC weekly Resume lenalidomide at next lower dose, continuously for Days 1 to 28 of repeated 28-day cycle.
If at the 5 mg daily dose, For a subsequent drop <30,000/mcL	Interrupt lenalidomide treatment. Do not dose below 5 mg dailyfor Day 1 to 21 of 28 day cycle.
Return to ≥30,000/mcL	Resume lenalidomide treatment at 5 mg daily for Days 1 to 21 of 28-day cycle. Do not dose below 5 mg daily for Day 1 to 21 of 28-day cycle.

Absolute Neutrophil Counts (ANC)
Neutropenia in MM

When Neutrophils	Recommended Course
Fall to <500/mcL Return to ≥500/mcL	Interrupt lenalidomide treatment, follow CBC weekly Resume lenalidomide capsule at next lower dose continuously for Days 1 to 28 of repeated 28-day cycle
If at the 5 mg daily dose, For a subsequent drop <500/mcL	Interrupt lenalidomide treatment. Do not dose below 5 mg daily for Day 1 to 21 of 28 day cycle.
Return to ≥500/mcL	Resume lenalidomide at 5 mg daily for Days 1 to 21 of 28-day cycle. Do not dose below 5 mg daily for Days 1 to 21 of 28-day cycle

Other Toxicities in MM

For other 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.

Starting Dose Adjustment for Renal Impairment in MM:

[See Dosage and Administration (2.4)].

2.2 Myelodysplastic Syndromes

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

Dose Adjustments for Hematologic Toxicities During MDS Treatment

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

Platelet counts

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

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

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

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

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

If thrombocytopenia develops during treatment at 5 mg daily in MDS

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

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

Absolute Neutrophil Counts (ANC)

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

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

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

When Neutrophils	Recommended Course

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 dexameth until progressive disease [Arm Rd Continuous; N=532] or for up to eighteen 28-day cycles [72 weeks, Arm Rd18; N=540] or who receive 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 (ra

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

In the Rd Continuous arm, the most common adverse reactions leading to dose interruption of lenalidomide were infection events (28.8%) of lenalidomide was 7 weeks. The most common adverse reactions leading to dose reduction of lenalidomide in the Rd Continuous arm time to the first dose reduction of lenalidomide was 16 weeks. In the Rd Continuous arm, the most common adverse reactions leading to (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 throughout treatment, except for cataracts. The frequency of onset of cataracts increased over time with 0.7% during the first 6 months Continuous.

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

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

Body System Adverse Reaction	All Adverse Reactions[a]			
	Rd Continuous (N = 532)	Rd18 (N = 540)	MPT (N = 541)	Rd Contin (N = 532)
General disorders and administration site conditions				
Fatigue%	173 (32.5)	177 (32.8)	154 (28.5)	39 (7.3)
Asthenia	150 (28.2)	123 (22.8)	124 (22.9)	41 (7.7)
Pyrexia[c]	114 (21.4)	102 (18.9)	76 (14.0)	13 (2.4)
Non-cardiac chest pain[f]	29 (5.5)	31 (5.7)	18 (3.3)	<1%
Gastrointestinal disorders				
Diarrhea	242 (45.5)	208 (38.5)	89 (16.5)	21 (3.9)
Abdominal pain[e,f]	109 (20.5)	78 (14.4)	60 (11.1)	7 (1.3)
Dyspepsia[f]	57 (10.7)	28 (5.2)	36 (6.7)	<1%
Musculoskeletal and connective tissue disorders				
Back pain[c]	170 (32)	145 (26.9)	116 (21.4)	37 (7)
Muscle spasms[f]	109 (20.5)	102 (18.9)	61 (11.3)	< 1%
Arthralgia[f]	101 (19.0)	71 (13.1)	66 (12.2)	9 (1.7)
Bone pain[f]	87 (16.4)	77 (14.3)	62 (11.5)	16 (3.0)
Pain in extremity[f]	79 (14.8)	66 (12.2)	61 (11.3)	8 (1.5)
Musculoskeletal pain[f]	67 (12.6)	59 (10.9)	36 (6.7)	< 1%
Musculoskeletal and connective tissue disorders				
Musculoskeletal chest pain[f]	60 (11.3)	51 (9.4)	39 (7.2)	6 (1.1)
Muscular weakness[f]	43 (8.1)	35 (6.5)	29 (5.4)	< 1%
Neck pain[f]	40 (7.5)	19 (3.5)	10 (1.8)	< 1%
Infections and infestations				
Bronchitis[c]	90 (16.9)	59 (10.9)	43 (7.9)	9 (1.7)
Nasopharyngitis[f]	80 (15.0)	54 (10.0)	33 (6.1)	0 (0.0)
Urinary tract infection[f]	76 (14.3)	63 (11.7)	41 (7.6)	8 (1.5)
Upper respiratory tract infection[c,g]	76 (14.3)	63 (11.7)	41 (7.6)	8 (1.5)
Pneumoniac[e]	93 (17.5)	87 (16.1)	56 (10.4)	60 (11.3)
Respiratory tract infection[h]	35 (6.6)	25 (4.6)	21 (3.9)	7 (1.3)
Influenza[f]	33 (6.2)	23 (4.3)	15 (2.8)	< 1%
Gastroenteritis[f]	32 (6.0)	17 (3.1)	13 (2.4)	0 (0.0)
Lower respiratory tract infection	29 (5.5)	14 (2.6)	16 (3.0)	10 (1.9)
Rhinitis[f]	29 (5.5)	24 (4.4)	14 (2.6)	0 (0.0)
Cellulitis[c]	< 5%	< 5%	< 5%	8 (1.5)
Sepsisc[e]	33 (6.2)	26 (4.8)	18 (3.3)	26 (4.9)
Nervous system disorders				
Headache[f]	75 (14.1)	52 (9.6)	56 (10.4)	< 1%
Dysgeusia[f]	39 (7.3)	45 (8.3)	22 (4.1)	< 1%
Blood and lymphatic system disorders[d]				
Anemia	233 (43.8)	193 (35.7)	229 (42.3)	97 (18.2
Neutropenia	186 (35.0)	178 (33.0)	328 (60.6)	148 (27.
Thrombocytopenia	104 (19.5)	100 (18.5)	135 (25.0)	44 (8.3)
Febrile neutropenia	7 (1.3)	17 (3.1)	15 (2.8)	6 (1.1)
Pancytopenia	5 (0.9)	6 (1.1)	7 (1.3)	1 (0.2)
Respiratory, thoracic and mediastinal disorders				
Cough[f]	121 (22.7)	94 (17.4)	68 (12.6)	< 1%
Dyspnea[c,e]	117 (22.0)	89 (16.5)	113 (20.9)	30 (5.6)
Epistaxis[f]	32 (6.0)	31 (5.7)	17 (3.1)	< 1%
Oropharyngeal pain[f]	30 (5.6)	22 (4.1)	14 (2.6)	0 (0.0)
Dyspnea exertional[e]	27 (5.1)	29 (5.4)	< 5%	6 (1.1)
Metabolism and nutrition disorders				
Decreased appetite	123 (23.1)	115 (21.3)	72 (13.3)	14 (2.6)
Hypokalemia[k]	91 (17.1)	62 (11.5)	38 (7)	35 (6.6)
Hyperglycemia	62 (11.7)	52 (9.6)	19 (3.5)	28 (5.3)
Hypocalcemia	57 (10.7)	56 (10.4)	31 (5.7)	23 (4.3)
Dehydration[k]	25 (4.7)	29 (5.4)	17 (3.1)	8 (1.5)
Gout[e]	< 5%	< 5%	< 5%	8 (1.5)
Diabetes mellitus[k,e]	< 5%	< 5%	< 5%	8 (1.5)
Hypophosphatemia[e]	< 5%	< 5%	< 5%	7 (1.3)
Hyponatremia[k,e]	< 5%	< 5%	< 5%	7 (1.3)
Skin and subcutaneous tissue disorders				
Rash	139 (26.1)	151 (28.0)	105 (19.4)	39 (7.3)
Pruritus[f]	47 (8.8)	49 (9.1)	24 (4.4)	< 1%
Psychiatric disorders				
Insomnia	147 (27.6)	127 (23.5)	53 (9.8)	4 (0.8)
Depression	58 (10.9)	46 (8.5)	30 (5.5)	10 (1.9)
Vascular disorders				
Deep vein thrombosis[c,k]	55 (10.3)	39 (7.2)	22 (4.1)	30 (5.6)
Hypotension[c,k]	51 (9.6)	35 (6.5)	36 (6.7)	11 (2.1)
Injury, Poisoning, and Procedural Complications				
Fall[f]	43 (8.1)	25 (4.6)	25 (4.6)	< 1%
Contusion[f]	33 (6.2)	24 (4.4)	15 (2.8)	< 1%
Eye disorders				
Cataract	73 (13.7)	31 (5.7)	5 (0.9)	31 (5.8)
Cataract subcapsular[e]	< 5%	< 5%	< 5%	7 (1.3)
Investigations				
Weight decreased	72 (13.5)	78 (14.4)	48 (8.9)	11 (2.1)
Cardiac disorders				
Atrial fibrillation[c]	37 (7.0)	25 (4.6)	25 (4.6)	13 (2.4)
Myocardial infarction (including acute)[c,e]	< 5%	< 5%	< 5%	10 (1.9)
Renal and Urinary disorders				
Renal failure (including acute)[c,e,i]	49 (9.2)	54 (10.0)	37 (6.8)	28 (5.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Squamous cell carcinoma[c,e]	< 5%	< 5%	< 5%	8 (1.5)
Basal cell carcinoma[c,e,f]	< 5%	< 5%	< 5%	< 1%

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

[a]All treatment-emergent adverse reactions in at least 5.0% of subjects in the Rd Continuous or Rd18 Arms and at least a 2.0% high Continuous or Rd18 Arms compared to the MPT Arm.

[b]All grade 3 or 4 treatment-emergent adverse reactions in at least 1.0% of subjects in the Rd Continuous or Rd18 Arms and at least the Rd Continuous or Rd18 Arms compared to the MPT Arm.

[c]Serious treatment-emergent adverse reactions in at least 1.0% of subjects in the Rd Continuous or Rd18 Arms and at least a 1.0% I 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 advers and have also been reported as serious.

[e]Footnote "a" not applicable

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

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

If thrombocytopenia develops during treatment at 5 mg daily in MDS

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

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

Absolute Neutrophil Counts (ANC)

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

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

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

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

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

If neutropenia develops during treatment at 5 mg daily in MDS

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

Other Grade 3 / 4 Toxicities in MDS

For other 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.

Starting Dose Adjustment for Renal Impairment in MDS

[See Dosage and Administration (2.4)].

2.3 Mantle Cell Lymphoma

The recommended starting dose of lenalidomide capsules is 25 mg/day orally on Days 1-21 of repeated 28-day cycles for relapsed or refractory mantle cell lymphoma.

Treatment should be continued until disease progression or unacceptable toxicity.
Treatment is continued, modified or discontinued based upon clinical and laboratory findings.

Dose Adjustments for Hematologic Toxicities During MCL Treatment

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

Platelet counts

Thrombocytopenia during treatment in MCL

When Platelets	Recommended Course
Fall to <50,000/mcL Return to ≥50,000/mcL	Interrupt lenalidomide capsules treatment and follow CBC weekly 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 to <1000/mcL for at least 7 days OR Falls to < 1,000/mcL with an associated temperature ≥ 38.5°C OR Falls to < 500 /mcL	Interrupt lenalidomide treatment and follow CBC weekly
Return to ≥1,000/mcL	Resume lenalidomide capsules at 5 mg less than the previous dose. Do not dose below 5 mg daily

Other Grade 3 / 4 Toxicities in MCL

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

Starting Dose Adjustment for Renal Impairment in MCL

[see Dosage and Administration (2.4)].

2.4 Starting Dose for Renal Impairment

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

Table 3: Starting Dose Adjustments for Patients with Renal Impairment

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

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 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)].

3 DOSAGE FORMS AND STRENGTHS

Lenalidomide capsules are available in the following strengths:

5 mg white opaque capsules printed with NAT on cap and 5 mg on body of the capsule.
10 mg white opaque capsules printed with NAT on cap and 10 mg on body of the capsule.
15 mg white opaque capsules printed with NAT on cap and 15 mg on body of the capsule.
25 mg white opaque capsules printed with NAT on cap and 25 mg on body of the capsule.

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 contraindicatec 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), 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 (5.7)]**.

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.

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 dur ng 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 *[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 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)]*.

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

Patients taking lenalidomide capsules for MDS should have their complete blood counts monitored weekly for the first 8 weeks and at least monthly thereafter. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the MDS study. In the 48% of patients who developed Grade 3 or 4 neutropenia, the median time to onset was 42 days (range, 14 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)]*.

Patients taking lenalidomide capsules for MCL should have their complete blood counts monitored 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.

5.3 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.

Contusion[f]	33 (6.2)	24 (4.4)	15 (2.8)	< 1%
Eye disorders				
Cataract	73 (13.7)	31 (5.7)	5 (0.9)	31 (5.8)
Cataract subcapsular[g]	< 5%	< 5%	< 5%	7 (1.3)
Investigations				
Weight decreased	72 (13.5)	78 (14.4)	48 (8.9)	11 (2.1)
Cardiac disorders				
Atrial fibrillation[c]	37 (7.0)	25 (4.6)	25 (4.6)	13 (2.4)
Myocardial infarction (including acute)[c,e]	< 5%	< 5%	< 5%	10 (1.9)
Renal and Urinary disorders				
Renal failure (including acute)[c,e,f]	49 (9.2)	54 (10.0)	37 (6.8)	28 (5.3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Squamous cell carcinoma[c,s]	< 5%	< 5%	< 5%	8 (1.5)
Basal cell carcinoma[c,e,f]	< 5%	< 5%	< 5%	< 1%

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

[a]All treatment-emergent adverse reactions in at least 5.0% of subjects in the Rd Continuous or Rd18 Arms and at least a 2.0% higl Continuous or Rd18 Arms compared to the MPT Arm.

[b]All grade 3 or 4 treatment-emergent adverse reactions in at least 1.0% of subjects in the Rd Continuous or Rd18 Arms and at leas the Rd Continuous or Rd18 Arms compared to the MPT Arm.

[c]Serious treatment-emergent adverse reactions in at least 1.0% of subjects in the Rd Continuous or Rd18 Arms and at least a 1.0% 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 adver and have also been reported as serious.

[e]Footnote "a" not applicable

[f]Footnote "b" not applicable.

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

[s] -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 include 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, pneum klebsiella, atypical pneumonia, pneumonia bacterial, pneumonia escherichia, pneumonia streptococcal, pneumonia viral

Sepsis: Sepsis, septic shock, urosepsis, escherichia sepsis, neutropenic sepsis, pneumococcal sepsis, staphylococcal sepsis, bacteri klebsiella sepsis, pseudomonal sepsis

Rash: Rash, rash pruritic, rash erythematous, rash maculo-papular, rash generalized, rash papular, exfoliative rash, rash follicular, ra 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) o In the lenalidomide/dexamethasone treatment group, 269 patients (76%) had at least one dose interruption with or without a dose reduc the placebo/dexamethasone treatment group. Of these patients who had one dose interruption with or without a dose reduction, 50% had at least one additional dose interruption with or without a dose reduction compared to 21% in the placebo/dexamethasone treatmen reactions were more frequent in patients who received the combination of lenalidomide /dexamethasone compared to placebo/dexam Tables 6, 7, and 8 summarize the adverse reactions reported for lenalidomide /dexamethasone and placebo/dexamethasone groups.

Table 6: Adverse Reactions Reported in ≥5% of Patients and with a ≥2% Difference in Proportion of Patients Between the Lenalid Groups

Body System Adverse Reaction	Lenalidomide/Dex* (N=353) n (%)	
Blood and lymphatic system disorders		
Neutropenia%	149 (42.2)	
Anemia[e]	111 (31.4)	
Thrombocytopenia[e]	76 (21.5)	
Leukopenia	28 (7.9)	
Lymphopenia	19 (5.4)	
General disorders and administration site conditions		
Fatigue	155 (43.9)	
Pyrexia	97 (27.5)	
Peripheral edema	93 (26.3)	
Chest Pain	29 (8.2)	
Lethargy	24 (6.8)	
Gastrointestinal disorders		
Constipation	143 (40.5)	
Diarrhea[e]	136 (38.5)	
Nausea[e]	92 (26.1)	
Vomiting[e]	43 (12.2)	
Abdominal Pain[e]	35 (9.9)	
Dry Mouth	25 (7.1)	
Musculoskeletal and connective tissue disorders		
Muscle cramp	118 (33.4)	
Back pain	91 (25.8)	
Bone Pain	48 (13.6)	
Pain in Limb	42 (11.9)	
Nervous system disorders		
Dizziness	82 (23.2)	
Tremor	75 (21.2)	
Dysgeusia	54 (15.3)	
Hypoesthesia	36 (10.2)	
Neuropathy[a]	23 (6.5)	
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	83 (23.5)	
Nasopharyngitis	62 (17.6)	
Pharyngitis	48 (13.6)	
Bronchitis	40 (11.3)	
Infections[b] and Infestations		
Upper respiratory tract infection	87 (24.6)	
Pneumonia[e]	48 (13.6)	
Urinary Tract Infection	30 (8.5)	
Sinusitis	26 (7.4)	
Skin and subcutaneous system disorders		
Rash[c]	75 (21.2)	
Sweating Increased	35 (9.9)	
Dry Skin	33 (9.3)	
Pruritus	27 (7.6)	
Metabolism and nutrition disorders		
Anorexia	55 (15.6)	
Hypokalemia	48 (13.6)	
Hypocalcemia	31 (8.8)	
Appetite Decreased	24 (6.8)	
Dehydration	23 (6.5)	
Hypomagnesemia	24 (6.8)	
Investigations		
Weight Decreased	69 (19.5)	
Eye disorders		
Blurred vision	61 (17.3)	
Vascular disorders		
Deep vein thrombosis[s]	33 (9.3)	
Hypertension	28 (7.9)	
Hypotension	25 (7.1)	

Table 7: Grade 3/4 Adverse Reactions Reported in ≥2% Patients and With a ≥1% Difference in Proportion of Patients Between the Le sone groups

Body System Adverse Reaction	Lenalidomide/Dex* (N=353) n (%)	
Blood and lymphatic system disorders		
Neutropenia[s]	118 (33.4)	
Thrombocytopenia[e]	43 (12.2)	
Anemia[e]	35 (9.9)	
Leukopenia	14 (4.0)	

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 *[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 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)]*.

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

Patients taking lenalidomide capsules for MDS should have their complete blood counts monitored weekly for the first 8 weeks and at least monthly thereafter. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the MDS study. In the 48% of patients who developed Grade 3 or 4 neutropenia, the median time to onset was 42 days (range, 14 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)]*.

Patients taking lenalidomide capsules for MCL should have their complete blood counts monitored 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.

5.3 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)].

5.4 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 – 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.

5.5 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 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.

5.6 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.

5.7 Hepatotoxicity
Hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dexamethasone. In clinical trials, 15% of patients experienced hepatotoxicity (with hepatocellular, cholestatic and mixed characteristics); 2% of patients with 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.

5.8 Severe Cutaneous Reactions Including Hypersensitivity Reactions
Angioedema and 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. Lenalidomide capsules interruption or discontinuation should be considered for Grade 2-3 skin rash. Lenalidomide capsules must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS, TEN or DRESS is suspected and should not be resumed following discontinuation for these reactions.

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

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

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

5.11 Impaired Stem Cell Mobilization
A decrease in the number of CD34+ cells collected after treatment (> 4 cycles) with 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.

5.12 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.

5.13 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 (≥10 x 10^9/L).

5 ADVERSE REACTIONS
The following adverse reactions are described in detail in other sections of the prescribing information:
- Embryo-Fetal Toxicity *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Hematologic Toxicity *[see Boxed Warning, Warnings and Precautions (5.2)]*
- Venous and Arterial Thromboembolism *[see Boxed Warning, Warnings and Precautions (5.3)]*
- Increased Mortality in Patients with CLL *[see Warnings and Precautions (5.4)]*
- Second Primary Malignancies *[see Warnings and Precautions (5.5)]*
- Increased Mortality in Patients with MM When Pembrolizumab Is Added to a Thalidomide Analogue and Dexamethasone [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 (5.6)*]
- Hepatotoxicity *[see Warnings and Precautions (5.7)]*
- Severe Cutaneous Reactions Including Hypersensitivity Reactions *[see Warnings and Precautions (5.8)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.9)]*
- Tumor Flare Reactions *[see Warnings and Precautions (5.10)]*
- Impaired Stem Cell Mobilization *[see Warnings and Precautions (5.11)]*
- Thyroid Disorders *[see Warnings and Precautions (5.12)]*
- Early Mortality in Patients with MCL *[see Warnings and Precautions (5.13)]*

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.

Investigations	
Weight Decreased	69 (19.5)
Eye disorders	
Blurred vision	61 (17.3)
Vascular disorders	
Deep vein thrombosis[%]	33 (9.3)
Hypertension	28 (7.9)
Hypotension	25 (7.1)

Table 7: Grade 3/4 Adverse Reactions Reported in ≥2% Patients and With a ≥1% Difference in Proportion of Patients Between t sone groups

Body System Adverse Reaction	**Lenalidomide/Dex[a]** **(N=353)** **n (%)**
Blood and lymphatic system disorders	
Neutropenia[%]	118 (33.4)
Thrombocytopenia[@]	43 (12.2)
Anemia[@]	35 (9.9)
Leukopenia	14 (4.0)
Lymphopenia	10 (2.8)
Febrile Neutropenia[%]	8 (2.3)
General disorders and administration site conditions	
Fatigue	23 (6.5)
Vascular disorders	
Deep vein thrombosis[%]	29 (8.2)
Infections and infestations	
Pneumonia[@]	30 (8.5)
Urinary Tract Infection	5 (1.4)
Metabolism and nutrition disorders	
Hypokalemia	17 (4.8)
Hypocalcemia	13 (3.7)
Hypophosphatemia	9 (2.5)
Respiratory, thoracic and mediastinal disorders	
Pulmonary embolism[@]	14 (4.0)
Respiratory Distress[@]	4 (1.1)
Musculoskeletal and connective tissue disorders	
Muscle weakness	20 (5.7)
Gastrointestinal disorders	
Diarrhea[@]	11 (3.1)
Constipation	7 (2.0)
Nausea[@]	6 (1.7)
Cardiac disorders	
Atrial fibrillation[@]	13 (3.7)
Tachycardia	6 (1.7)
Cardiac Failure Congestive[@]	5 (1.4)
Nervous System disorders	
Syncope	10 (2.8)
Dizziness	7 (2.0)
Eye disorders	
Cataract	6 (1.7)
Cataract Unilateral	5 (1.4)
Psychiatric Disorder	
Depression	10 (2.8)

Table 8: Serious Adverse Reactions Reported in ≥1% Patients and With a ≥1% Difference in Proportion of Pat Placebo/dexamethasone Groups

Body System Adverse Reaction	**Lenalidomide/Dex[a]** **(N=353)** **n (%)**
Blood and lymphatic system disorders	
Febrile Neutropenia[%]	6 (1.7)
Vascular disorders	
Deep vein thrombosis[%]	26 (7.4)
Infections and infestations	
Pneumonia[@]	33 (9.3)
Respiratory, thoracic and mediastinal disorders	
Pulmonary embolism[@]	13 (3.7)
Cardiac disorders	
Atrial fibrillation[@]	11 (3.1)
Cardiac Failure Congestive[@]	5 (1.4)
Nervous System disorders	
Cerebrovascular accident[@]	(2.0)
Gastrointestinal disorders	
Diarrhea[@]	6 (1.7)
Musculoskeletal and connective tissue disorders	
Bone Pain	4 (1.1)

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 inc

Median duration of exposure among patients treated with lenalidomide/dexamethasone was 44 weeks while median duration of sone was 23 weeks. This should be taken into consideration when comparing frequency of adverse reactions between two treatm methasone

Venous and Arterial Thromboembolism [see Boxed Warning, Warnings and Precautions (5.3)]
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 lenalid the placebo/dexamethasone group, respectively in the 2 studies in patients with at least 1 prior therapy with discontinuations d between groups. In the NDMM study, DVT was reported as an adverse reaction (all grades: 10.3%, 7.2%, 4.1%), as a serious adve reaction (5.6%, 3.7%, 2.8%) in the Rd Continuous, Rd18, and MPT Arms, respectively. Discontinuations and dose reductions due to between the Rd Continuous and Rd18 Arms (both <1%). Interruption of Lenalidomide treatment due to DVT adverse reactions wa (2.3%) and Rd18 (1.5%) arms.

Date of Issue 19 - 12 - 2018
Description LIDAMID PIL (50 x 100 cm)

	NATCO Approval		PHARMALINE Approval	
	Regulatory (Local)	Quality Assurance	Regulatory	Quality Assurance
Name			Rajaa Daouk	Josephine Abi Habib
Signature				
Date			15/01/2018	21/12/2018

ɔtion Therapy:
study who received at least one dose of lenalidomide with low dose dexamethasone (Rd) given for 2 different durations of time (i.e., or up to eighteen 28-day cycles (72 weeks, Arm Rd18; N=540) or who received melphalan, prednisone and thalidomide (Arm MPT; 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).

were comparable in Arm Rd Continuous and Arm Rd18, and included diarrhea, anemia, constipation, peripheral edema, neutropenia, ıst frequently reported Grade 3 or 4 reactions included neutropenia, anemia, thrombocytopenia, pneumonia, asthenia, fatigue, back DVT, hyperglycemia, and leukopenia. The highest frequency of infections occurred in Arm Rd Continuous (75%) compared to Arm dverse reactions of infection in Arm Rd Continuous than either Arm MPT or Rd18.

ons leading to dose interruption of lenalidomide were infection events (28.8%); overall, the median time to the first dose interruption reactions leading to dose reduction of lenalidomide in the Rd Continuous arm were hematologic events (10.7%); overall, the median ks. In the Rd Continuous arm, the most common adverse reactions leading to discontinuation of lenalidomide were infection events

tions were generally highest in the first 6 months of treatment and then the frequencies decreased over time or remained stable 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

Rd Continuous, Rd18, and MPT treatment arms.

dverse Reactions in ≥ 1.0% of Patients in the Rd Continuous or Rd18 Arms*

All Adverse Reactions*			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)
tions					
173 (32.5)	177 (32.8)	154 (28.5)	39 (7.3)	46 (8.5)	31 (5.7)
150 (28.2)	123 (22.8)	124 (22.9)	41 (7.7)	33 (6.1)	32 (5.9)
114 (21.4)	102 (18.9)	76 (14.0)	13 (2.4)	7 (1.3)	7 (1.3)
29 (5.5)	31 (5.7)	18 (3.3)	<1%	< 1%	< 1%
242 (45.5)	208 (38.5)	89 (16.5)	21 (3.9)	18 (3.3)	8 (1.5)
109 (20.5)	78 (14.4)	60 (11.1)	7 (1.3)	9 (1.7)	< 1%
57 (10.7)	28 (5.2)	36 (6.7)	<1%	< 1%	0 (0.0)
s					
170 (32)	145 (26.9)	116 (21.4)	37 (7)	34 (6.3)	28 (5.2)
109 (20.5)	102 (18.9)	61 (11.3)	< 1%	< 1%	< 1%
101 (19.0)	71 (13.1)	66 (12.2)	9 (1.7)	8 (1.5)	8 (1.5)
87 (16.4)	77 (14.3)	62 (11.5)	16 (3.0)	15 (2.8)	14 (2.6)
79 (14.8)	66 (12.2)	6* (11.3)	8 (1.5)	8 (1.5)	7 (1.3)
67 (12.6)	59 (10.9)	36 (6.7)	< 1%	< 1%	< 1%
s					
60 (11.3)	51 (9.4)	39 (7.2)	6 (1.1)	< 1%	< 1%
43 (8.1)	35 (6.5)	29 (5.4)	< 1%	8 (1.5)	< 1%
40 (7.5)	19 (3.5)	10 (1.8)	< 1%	< 1%	< 1%
90 (16.9)	59 (10.9)	43 (7.9)	9 (1.7)	6 (1.1)	3 (0.6)
80 (15.0)	54 (10.0)	33 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)
76 (14.3)	63 (11.7)	41 (7.6)	8 (1.5)	8 (1.5)	< 1%
76 (14.3)	63 (11.7)	41 (7.6)	8 (1.5)	8 (1.5)	< 1%
93 (17.5)	87 (16.1)	56 (10.4)	60 (11.3)	57 (10.5)	41 (7.6)
35 (6.6)	25 (4.6)	21 (3.9)	7 (1.3)	4 (0.7)	1 (0.2)
33 (6.2)	23 (4.3)	15 (2.8)	< 1%	< 1%	0 (0.0)
32 (6.0)	17 (3.1)	13 (2.4)	0 (0.0)	< 1%	< 1%
29 (5.5)	14 (2.6)	16 (3.0)	10 (1.9)	3 (0.6)	3 (0.6)
29 (5.5)	24 (4.4)	14 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
< 5%	< 5%	< 5%	8 (1.5)	3 (0.6)	2 (0.4)
33 (6.2)	26 (4.8)	18 (3.3)	26 (4.9)	20 (3.7)	13 (2.4)
75 (14.1)	52 (9.6)	56 (10.4)	< 1%	< 1%	< 1%
39 (7.3)	45 (8.3)	22 (4.1)	< 1%	0 (0.0)	< 1%
233 (43.8)	193 (35.7)	229 (42.3)	97 (18.2)	85 (15.7)	102 (18.9)
186 (35.0)	178 (33.0)	328 (60.6)	148 (27.8)	143 (26.5)	243 (44.9)
104 (19.5)	100 (18.5)	135 (25.0)	44 (8.3)	43 (8.0)	60 (11.1)
7 (1.3)	17 (3.1)	15 (2.8)	6 (1.1)	16 (3.0)	14 (2.6)
5 (0.9)	6 (1.1)	7 (1.3)	1 (0.2)	3 (0.6)	5 (0.9)
121 (22.7)	94 (17.4)	68 (12.6)	< 1%	< 1%	< 1%
117 (22.0)	89 (16.5)	113 (20.9)	30 (5.6)	22 (4.1)	18 (3.3)
32 (6.0)	31 (5.7)	17 (3.1)	< 1%	< 1%	0 (0.0)
30 (5.6)	22 (4.1)	14 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
27 (5.1)	29 (5.4)	< 5%	6 (1.1)	0 (0.0)	0 (0.0)
123 (23.1)	115 (21.3)	72 (13.3)	14 (2.6)	7 (1.3)	5 (0.9)
91 (17.1)	62 (11.5)	38 (7)	35 (6.6)	20 (3.7)	11 (2.0)
62 (11.7)	52 (9.6)	19 (3.5)	28 (5.3)	23 (4.3)	9 (1.7)
57 (10.7)	56 (10.4)	31 (5.7)	23 (4.3)	19 (3.5)	8 (1.5)
25 (4.7)	29 (5.4)	17 (3.1)	8 (1.5)	13 (2.4)	9 (1.7)
< 5%	< 5%	< 5%	8 (1.5)	0 (0.0)	0 (0.0)
< 5%	< 5%	< 5%	8 (1.5)	4 (0.7)	2 (0.4)
< 5%	< 5%	< 5%	7 (1.3)	3 (0.6)	1 (0.2)
< 5%	< 5%	< 5%	7 (1.3)	13 (2.4)	6 (1.1)
139 (26.1)	151 (28.0)	105 (19.4)	39 (7.3)	38 (7.0)	33 (6.1)
47 (8.8)	49 (9.1)	24 (4.4)	< 1%	< 1%	< 1%
147 (27.6)	127 (23.5)	53 (9.8)	4 (0.8)	6 (1.1)	0 (0.0)
58 (10.9)	46 (8.5)	30 (5.5)	10 (1.9)	4 (0.7)	1 (0.2)
55 (10.3)	39 (7.2)	22 (4.1)	30 (5.6)	20 (3.7)	15 (2.8)
51 (9.6)	35 (6.5)	36 (6.7)	11 (2.1)	8 (1.5)	6 (1.1)
43 (8.1)	25 (4.6)	25 (4.6)	< 1%	6 (1.1)	6 (1.1)
33 (6.2)	24 (4.4)	15 (2.8)	< 1%	< 1%	0 (0.0)
73 (13.7)	31 (5.7)	5 (0.9)	31 (5.8)	14 (2.6)	3 (0.6)
< 5%	< 5%	< 5%	7 (1.3)	0 (0.0)	0 (0.0)
72 (13.5)	78 (14.4)	48 (8.9)	11 (2.1)	4 (0.7)	4 (0.7)
37 (7.0)	25 (4.6)	25 (4.6)	13 (2.4)	9 (1.7)	6 (1.1)
< 5%	< 5%	< 5%	10 (1.9)	3 (0.6)	5 (0.9)
49 (9.2)	54 (10.0)	37 (6.8)	28 (5.3)	33 (6.1)	29 (5.4)
incl cysts and polyps)					
< 5%	< 5%	< 5%	8 (1.5)	4 (0.7)	0 (0.0)
< 5%	< 5%	< 5%	< 1%	< 1%	0 (0.0)

eaction is counted only once under the applicable Body System/Adverse Reaction.
t 5.0% of subjects in the Rd Continuous or Rd18 Arms and at least a 2.0% higher frequency (%) in either the Rd
.
ons in at least 1.0% of subjects in the Rd Continuous or Rd18 Arms and at least a 1.0% higher frequency (%) in either PT Arm.
t least 1.0% of subjects in the Rd Continuous or Rd18 Arms and at least a 1.0% higher frequency (%) in either the Rd
.
disorders body system were included by medical judgment as known adverse reactions for Rd Continuous/Rd18,

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 ≥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 event 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 events were related to blood and lymphatic system disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders, and general disorders and administrative site conditions.
Thrombocytopenia (61.5%; 91/148) and neutropenia (58.8%; 87/148) were the most frequently reported adverse events. The next most common adverse events observed were diarrhea (48.6%; 72/148), pruritus (41.9%; 62/148), rash (35.8%; 53/148) and fatigue (31.1%; 46/148). Table 9 summarizes the adverse events that were reported in ≥ 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 events that are drug-related and those that reflect the patient's underlying disease.

Table 9: Summary of Adverse Events Reported in ≥5% of the Lenalidomide Treated Patients in del 5q MDS Clinical Study

Body System Adverse Event[a]	10 mg Overall (N=148)	
Patients with at least one adverse event	148	(100.0)
Blood and Lymphatic System Disorders		
Thrombocytopenia	91	(61.5)
Neutropenia	87	(58.8)
Anemia	17	(11.5)
Leukopenia	12	(8.1)
Febrile Neutropenia	8	(5.4)
Skin and Subcutaneous Tissue Disorders		
Pruritus	62	(41.9)
Rash	53	(35.8)
Dry Skin	21	(14.2)
Contusion	12	(8.1)
Night Sweats	12	(8.1)
Sweating Increased	10	(6.8)
Ecchymosis	8	(5.4)
Erythema	8	(5.4)
Gastrointestinal Disorders		
Diarrhea	72	(48.6)
Constipation	35	(23.6)
Nausea	35	(23.6)
Abdominal Pain	18	(12.2)
Vomiting	15	(10.1)
Abdominal Pain Upper	12	(8.1)
Dry Mouth	10	(6.8)
Loose Stools	9	(6.1)
Respiratory, Thoracic and Mediastinal Disorders		
Nasopharyngitis	34	(23.0)
Cough	29	(19.6)
Dyspnea	25	(16.9)
Pharyngitis	23	(15.5)
Epistaxis	22	(14.9)
Dyspnea Exertional	10	(6.8)
Rhinitis	10	(6.8)
Bronchitis	9	(6.1)
General Disorders and Administration Site Conditions		
Fatigue	46	(31.1)
Pyrexia	31	(20.9)
Edema Peripheral	30	(20.3)
Asthenia	22	(14.9)
Edema	15	(10.1)
Pain	10	(6.8)
Rigors	9	(6.1)
Chest Pain	8	(5.4)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	32	(21.6)
Back Pain	31	(20.9)
Muscle Cramp	27	(18.2)
Pain in Limb	16	(10.8)
Myalgia	13	(8.8)
Peripheral Swelling	12	(8.1)
Nervous System Disorders		
Dizziness	29	(19.6)
Headache	29	(19.6)
Hypoesthesia	10	(6.8)
Dysgeusia	9	(6.1)
Peripheral Neuropathy	8	(5.4)
Infections and Infestations		
Upper Respiratory Tract Infection	22	(14.9)
Pneumonia	17	(11.5)
Urinary Tract Infection	16	(10.8)
Sinusitis	12	12
Cellulitis	8	(5.4)
Metabolism and Nutrition Disorders		
Hypokalemia	16	(10.8)
Anorexia	15	(10.1)
Hypomagnesemia	9	(6.1)
Investigations		
Alanine Aminotransferase Increased	12	(8.1)
Psychiatric Disorders		
Insomnia	15	(10.1)
Depression	8	(5.4)
Renal and Urinary Disorders		
Dysuria	10	(6.8)

25 (4.6)	25 (4.6)	< 1%	6 (1.1)	6 (1.1)
24 (4.4)	15 (2.8)	< 1%	< 1%	0 (0.0)
31 (5.7)	5 (0.9)	31 (5.8)	14 (2.6)	3 (0.6)
< 5%	< 5%	7 (1.3)	0 (0.0)	0 (0.0)
78 (14.4)	48 (8.9)	11 (2.1)	4 (0.7)	4 (0.7)
25 (4.6)	25 (4.6)	13 (2.4)	9 (1.7)	6 (1.1)
< 5%	< 5%	10 (1.9)	3 (0.6)	5 (0.9)
54 (10.0)	37 (6.8)	28 (5.3)	33 (6.1)	29 (5.4)
ps)				
< 5%	< 5%	8 (1.5)	4 (0.7)	0 (0.0)
< 5%	< 5%	< 1%	< 1%	0 (0.0)

)nly once under the applicable Body System/Adverse Reaction.
n the Rd Continuous or Rd18 Arms and at least a 2.0% higher frequency (%) in either the Rd

of subjects in the Rd Continuous or Rd18 Arms and at least a 1.0% higher frequency (%) in either

cts in the Rd Continuous or Rd18 Arms and at least a 1.0% higher frequency (%) in either the Rd

stem were included by medical judgment as known adverse reactions for Rd Continuous/Rd18,

-atening (if the outcome

r, gastrointestinal pain
chopneumonia, pneumocystis jiroveci pneumonia, pneumonia legionella, pneumonia staphylococcal, pneumonia
pneumonia streptococcal, pneumonia viral
sis, pneumococcal sepsis, staphylococcal sepsis, bacterial sepsis, meningococcal sepsis, enterococcal sepsis,

eralized, rash papular, exfoliative rash, rash follicular, rash macular, drug rash with eosinophilia and systemic

us thrombosis

ne dose of lenalidomide /dexamethasone (353 patients) or placebo/dexamethasone (350 patients).
at least one dose interruption with or without a dose reduction of lenalidomide compared to 199 patients (57%) in
e dose interruption with or without a dose reduction, 50% in the lenalidomide /dexamethasone treatment group
compared to 21% in the placebo/dexamethasone treatment group. Most adverse reactions and Grade 3/4 adverse
alidomide /dexamethasone compared to placebo/dexamethasone.
/dexamethasone and placebo/dexamethasone groups.

fference in Proportion of Patients Between the Lenalidomide/dexamethasone and Placebo/dexamethasone

Lenalidomide/Dex* (N=353) n (%)	Placebo/Dex * (N=350) n (%)
149 (42.2)	22 (6.3)
111 (31.4)	83 (23.7)
76 (21.5)	37 (10.6)
28 (7.9)	4 (1.1)
19 (5.4)	5 (1.4)
155 (43.9)	146 (41.7)
97 (27.5)	82 (23.4)
93 (26.3)	74 (21.1)
29 (8.2)	20 (5.7)
24 (6.8)	8 (2.3)
143 (40.5)	74 (21.1)
136 (38.5)	96 (27.4)
92 (26.1)	75 (21.4)
43 (12.2)	33 (9.4)
35 (9.9)	22 (6.3)
25 (7.1)	13 (3.7)
118 (33.4)	74 (21.1)
91 (25.8)	65 (18.6)
48 (13.6)	39 (11.1)
42 (11.9)	32 (9.1)
82 (23.2)	59 (16.9)
75 (21.2)	26 (7.4)
54 (15.3)	34 (9.7)
36 (10.2)	25 (7.1)
23 (6.5)	13 (3.7)
83 (23.5)	60 (17.1)
62 (17.6)	31 (8.9)
48 (13.6)	33 (9.4)
40 (11.3)	30 (8.6)
87 (24.6)	55 (15.7)
48 (13.6)	29 (8.3)
30 (8.5)	19 (5.4)
26 (7.4)	16 (4.6)
75 (21.2)	33 (9.4)
35 (9.9)	25 (7.1)
33 (9.3)	14 (4.0)
27 (7.6)	18 (5.1)
55 (15.6)	34 (9.7)
48 (13.6)	21 (6.0)
31 (8.8)	10 (2.9)
24 (6.8)	14 (4.0)
23 (6.5)	15 (4.3)
24 (6.8)	10 (2.9)
69 (19.5)	52 (14.9)
61 (17.3)	40 (11.4)
33 (9.3)	15 (4.3)
28 (7.9)	20 (5.7)
25 (7.1)	15 (4.3)

≥1% Difference in Proportion of Patients Between the Lenalidomide/dexmethasone and Placebo/dexametha-

Lenalidomide/Dex* (N=353) n (%)	Placebo/Dex * (N=350) n (%)
118 (33.4)	12 (3.4)
43 (12.2)	22 (6.3)
35 (9.9)	20 (5.7)
14 (4.0)	1 (0.3)

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

[1] Body System and adverse events are coded using the MedDRA dictionary. Body System and adverse events are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Table 10: Most Frequently Observed Grade 3 and 4 Adverse Events [1]
Regardless of Relationship to Study Drug Treatment

Adverse Events [2]	10 mg (N=148)
Patients with at least one Grade 3/4 AE	131 (88.5)
Neutropenia	79 (53.4)
Thrombocytopenia	74 (50.0)
Pneumonia	11 (7.4)
Rash	10 (6.8)
Anemia	9 (6.1)
Leukopenia	8 (5.4)
Fatigue	7 (4.7)
Dyspnea	7 (4.7)
Back pain	7 (4.7)
Febrile Neutropenia	6 (4.1)
Nausea	6 (4.1)
Diarrhea	5 (3.4)
Pyrexia	5 (3.4)
Sepsis	4 (2.7)
Dizziness	4 (2.7)
Granulocytopenia	3 (2.0)
Chest Pain	3 (2.0)
Pulmonary Embolism	3 (2.0)
Respiratory Distress	3 (2.0)
Pruritus	3 (2.0)
Pancytopenia	3 (2.0)
Muscle Cramp	3 (2.0)
Respiratory Tract Infection	2 (1.4)
Upper Respiratory Tract Infection	2 (1.4)
Asthenia	2 (1.4)
Multi-organ Failure	2 (1.4)
Epistaxis	2 (1.4)
Hypoxia	2 (1.4)
Pleural Effusion	2 (1.4)
Pneumonitis	2 (1.4)
Pulmonary Hypertension	2 (1.4)
Vomiting	2 (1.4)
Sweating Increased	2 (1.4)
Arthralgia	2 (1.4)
Pain in Limb	2 (1.4)
Headache	2 (1.4)
Syncope	2 (1.4)

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

In other clinical studies of lenalidomide in MDS patients, the following serious adverse events (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

Fall[f]	43 (8.1)	25 (4.6)	25 (4.6)	< 1%	6 (1.1)	6 (1.1)
Contusion[f]	33 (6.2)	24 (4.4)	15 (2.8)	< 1%	< 1%	0 (0.0)
Eye disorders						
Cataract	73 (13.7)	31 (5.7)	5 (0.9)	31 (5.8)	14 (2.6)	3 (0.6)
Cataract subcapsular[e]	< 5%	< 5%	< 5%	7 (1.3)	0 (0.0)	0 (0.0)
Investigations						
Weight decreased	72 (13.5)	78 (14.4)	48 (8.9)	11 (2.1)	4 (0.7)	4 (0.7)
Cardiac disorders						
Atrial fibrillation[c]	37 (7.0)	25 (4.6)	25 (4.6)	13 (2.4)	9 (1.7)	6 (1.1)
Myocardial infarction (including acute)[c,e]	< 5%	< 5%	< 5%	10 (1.9)	3 (0.6)	5 (0.9)
Renal and Urinary disorders						
Renal failure (including acute)[c,e,i]	49 (9.2)	54 (10.0)	37 (6.8)	28 (5.3)	33 (6.1)	29 (5.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Squamous cell carcinoma[c,e]	< 5%	< 5%	< 5%	8 (1.5)	4 (0.7)	0 (0.0)
Basal cell carcinoma[c,j]	< 5%	< 5%	< 5%	< 1%	< 1%	0 (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 reactions in at least 5.0% of subjects in the Rd Continuous or Rd18 Arms and at least a 2.0% higher frequency (%) in either the Rd Continuous or Rd18 Arms compared to the MPT Arm.

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

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

[e]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.

[f]Footnote "a" not applicable

[i]Footnote "b" not applicable.

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

[c] -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 include 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 ≥5% of Patients and with a ≥2% Difference in Proportion of Patients 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%	149 (42.2)	22 (6.3)
Anemia[e]	111 (31.4)	83 (23.7)
Thrombocytopenia[e]	76 (21.5)	37 (10.6)
Leukopenia	28 (7.9)	4 (1.1)
Lymphopenia	19 (5.4)	5 (1.4)
General disorders and administration site conditions		
Fatigue	155 (43.9)	146 (41.7)
Pyrexia	97 (27.5)	82 (23.4)
Peripheral edema	93 (26.3)	74 (21.1)
Chest Pain	29 (8.2)	20 (5.7)
Lethargy	24 (6.8)	8 (2.3)
Gastrointestinal disorders		
Constipation	143 (40.5)	74 (21.1)
Diarrhea[e]	136 (38.5)	96 (27.4)
Nausea[e]	92 (26.1)	75 (21.4)
Vomiting[e]	43 (12.2)	33 (9.4)
Abdominal Pain[e]	35 (9.9)	22 (6.3)
Dry Mouth	25 (7.1)	13 (3.7)
Musculoskeletal and connective tissue disorders		
Muscle cramp	118 (33.4)	74 (21.1)
Back pain	91 (25.8)	65 (18.6)
Bone Pain	48 (13.6)	39 (11.1)
Pain in Limb	42 (11.9)	32 (9.1)
Nervous system disorders		
Dizziness	82 (23.2)	59 (16.9)
Tremor	75 (21.2)	26 (7.4)
Dysgeusia	54 (15.3)	34 (9.7)
Hypoesthesia	36 (10.2)	25 (7.1)
Neuropathy[e]	23 (6.5)	13 (3.7)
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	83 (23.5)	60 (17.1)
Nasopharyngitis	62 (17.6)	31 (8.9)
Pharyngitis	48 (13.6)	33 (9.4)
Bronchitis	40 (11.3)	30 (8.6)
Infections[b] and infestations		
Upper respiratory tract infection	87 (24.6)	55 (15.7)
Pneumonia[e]	48 (13.6)	29 (8.3)
Urinary Tract Infection	30 (8.5)	19 (5.4)
Sinusitis	26 (7.4)	16 (4.6)
Skin and subcutaneous system disorders		
Rash[c]	75 (21.2)	33 (9.4)
Sweating Increased	35 (9.9)	25 (7.1)
Dry Skin	33 (9.3)	14 (4.0)
Pruritus	27 (7.6)	18 (5.1)
Metabolism and nutrition disorders		
Anorexia	55 (15.6)	34 (9.7)
Hypokalemia	48 (13.6)	21 (6.0)
Hypocalcemia	31 (8.8)	10 (2.9)
Appetite Decreased	24 (6.8)	14 (4.0)
Dehydration	23 (6.5)	15 (4.3)
Hypomagnesemia	24 (6.8)	10 (2.9)
Investigations		
Weight Decreased	69 (19.5)	52 (14.9)
Eye disorders		
Blurred vision	61 (17.3)	40 (11.4)
Vascular disorders		
Deep vein thrombosis%	33 (9.3)	15 (4.3)
Hypertension	28 (7.9)	20 (5.7)
Hypotension	25 (7.1)	15 (4.3)

Table 7: Grade 3/4 Adverse Reactions Reported in ≥2% Patients and With a ≥1% Difference in Proportion of Patients Between the Lenalidomide/dexmethasone 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 (33.4)	12 (3.4)
Thrombocytopenia[e]	43 (12.2)	22 (6.3)
Anemia[e]	35 (9.9)	20 (5.7)
Leukopenia	14 (4.0)	1 (0.3)
Nervous System Disorders		
Dizziness		
Headache		
Hypoesthesia		
Dysgeusia		
Peripheral Neuropathy		
Infections and Infestations		
Upper Respiratory Tract Infection		
Pneumonia		
Urinary Tract Infection		
Sinusitis		
Cellulitis		
Metabolism and Nutrition Disorders		
Hypokalemia		
Anorexia		
Hypomagnesemia		
Investigations		
Alanine Aminotransferase Increased		
Psychiatric Disorders		
Insomnia		
Depression		
Renal and Urinary Disorders		
Dysuria		
Vascular Disorders		
Hypertension		
Endocrine Disorders		
Acquired Hypothyroidism		
Cardiac Disorders		
Palpitations		

[x] Body System and adverse events are coded using the MedDRA dictionary. Body with multiple occurrences of an AE is counted only once in the AE category.

Table 10: Most Frequently Observed Grade 3 and 4 Adverse Events [1] Regardless of Relationship to Study Drug Treatment

Adverse Events [2]
Patients with at least one Grade 3/4 AE
Neutropenia
Thrombocytopenia
Pneumonia
Rash
Anemia
Leukopenia
Fatigue
Dyspnea
Back pain
Febrile Neutropenia
Nausea
Diarrhea
Pyrexia
Sepsis
Dizziness
Granulocytopenia
Chest Pain
Pulmonary Embolism
Respiratory Distress
Pruritus
Pancytopenia
Muscle Cramp
Respiratory Tract Infection
Upper Respiratory Tract Infection
Asthenia
Multi-organ Failure
Epistaxis
Hypoxia
Pleural Effusion
Pneumonitis
Pulmonary Hypertension
Vomiting
Sweating Increased
Arthralgia
Pain in Limb
Headache
Syncope

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

[2] Adverse events are coded using the MedDRA dictionary. A patient with multiple of an AE is counted only once in the adverse event category.

In other clinical studies of lenalidomide in MDS patients, the following serious adve

Blood and lymphatic system disorders: warm type hemolytic anemia, splenic infa

Cardiac disorders: cardiac failure congestive, atrial fibrillation, angina pectoris, ischemia, atrial fibrillation aggravated, bradycardia, cardiogenic shock, pulmonary

Ear and labyrinth disorders: vertigo

Endocrine disorders: Basedow's disease

Gastrointestinal disorders: gastrointestinal hemorrhage, colitis ischemic, intestinal ageal reflux disease, obstructive inguinal hernia, irritable bowel syndrome, melen gastrointestinal hemorrhage

General disorders and administration site conditions: disease progression, fall, g

Hepatobiliary disorders: hyperbilirubinemia, cholecystitis, acute cholecystitis, hep

Immune system disorders: hypersensitivity

Infections and infestations: infection bacteremia, central line infection, clostridial infection, *Klebsiella sepsis*, lobar pneumonia, localized infection, oral infection, *Ps*

Injury, poisoning and procedural complications: femur fracture, transfusion reactic hemorrhage, rib fracture, road traffic accident, spinal compression fracture

Investigations: blood creatinine increased, hemoglobin decreased, liver function t

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

Musculoskeletal and connective tissue disorders: arthritis, arthritis aggravated, g

Neoplasms benign, malignant and unspecified: acute leukemia, acute myeloid le

Nervous system disorders: cerebrovascular accident, aphasia, cerebellar infarct subarachnoid hemorrhage, transient ischemic attack

Psychiatric disorders: confusional state

Renal and urinary disorders: renal failure, hematuria, renal failure acute, azotemia

Reproductive system and breast disorders: pelvic pain

Respiratory, thoracic and mediastinal disorders: bronchitis, chronic obstructiv infiltration, wheezing

Skin and subcutaneous tissue disorders: acute febrile neutrophilic dermatosis

Vascular system disorders: deep vein thrombosis, hypotension, aortic disorder, is

m during any sexual contact with females of reproductive
undergone a successful vasectomy. Male patients taking

) because the blood might be given to a pregnant female

ction. Advise patients to observe for bleeding or bruising,
ave their complete blood counts assessed periodically as

) assessed every 7 days (weekly) for the first 2 cycles, on
Dosage and Administration (2.1)].

ind at least monthly thereafter. Grade 3 or 4 hematologic
median time to onset was 42 days (range, 14 to 411 days),
thrombocytopenia, the median time to onset was 28 days
Dosage and Administration (2.2)].

ys), every 2 weeks during cycles 2 to 4, and then monthly
43% of the patients. Grade 3 or 4 thrombocytopenia was

increased in patients treated with lenalidomide.

e treated with lenalidomide and dexamethasone therapy
ulant therapies. In the newly diagnosed multiple myeloma
.5%, 2.0%, and 1.7%) in the Rd Continuous, Rd18, and MPT
s (3.8%, 2.8%, and 3.7%, respectively) [see Boxed Warning

d with lenalidomide capsules and dexamethasone therapy
rction (including acute) was reported as a serious adverse
of CVA was similar between the Rd Continuous, Rd18, and

all modifiable factors (e.g. hyperlipidemia, hypertension,

DRA Query Embolic and Thrombotic events) occurred in
ombosis in patients treated with placebo and dexametha-
tic prophylaxis, the overall frequency of thrombotic events
osis event was 4.3 months in the combined Rd Continuous

derlying risks. Instruct patients to report immediately any
se should be based on a benefit-risk decision in patients

alidomide capsules therapy increased the risk of death as
s treatment arm compared to 18 deaths among 211 patients
in the risk of death. The trial was halted for safety in July

frequently in the lenalidomide capsules treatment arm.

y malignancies (SPM) notably AML and MDS have been
le capsules in combination with oral melphalan compared
1M treated with lenalidomide capsules in combination with

solid tumor (excluding squamous cell carcinoma and basal
cell carcinoma and basal cell carcinoma, occurred in 3.1%

an patients treated in the fixed duration lenalidomide-con-
of lenalidomide capsules and the risk of second primary

ne, a use for which no PD-1 or PD-L1 blocking antibody is
with a thalidomide analogue plus dexamethasone is not

ical trials, 15% of patients experienced hepatotoxicity (with
s hepatotoxicity events. The mechanism of drug-induced
be risk factors. Monitor liver enzymes periodically. Stop

drug reaction with eosinophilia and systemic symptoms
ver, and/or lymphadenopathy with systemic complications
rade 4 rash associated with thalidomide treatment should
in rash. Lenalidomide capsules must be discontinued for
liscontinuation for these reactions.

rsis syndrome are those with high tumor burden prior to

der lymph node swelling, low grade fever, pain and rash.

ogression of disease (PD). In the MCL trial, 13/134 (10%) of
TFR again in cycle 11. Lenalidomide may be continued in
R may also be treated with corticosteroids, non-steroidal
is recommended to withhold treatment with lenalidomide
reatment of Grade 1 and 2 TFR.

are auto-HSCT candidates, referral to a transplant center
enalidomide-containing treatment or for whom inadequate
CXCR4 inhibitor may be considered.

of lenalidomide capsules treatment and during therapy.

ol arm. On exploratory multivariate analysis, risk factors for

rnings and *Precautions (5.6)]*
rnings and *Precautions (5.6)]*

g cannot be directly compared to rates in the clinical trials

Investigations		
Weight Decreased	69 (19.5)	52 (14.9)
Eye disorders		
Blurred vision	61 (17.3)	40 (11.4)
Vascular disorders		
Deep vein thrombosis[%]	33 (9.3)	15 (4.3)
Hypertension	28 (7.9)	20 (5.7)
Hypotension	25 (7.1)	15 (4.3)

Table 7: Grade 3/4 Adverse Reactions Reported in ≥2% Patients and With a ≥1% Difference in Proportion of Patients Between the Lenalidomide/dexmethasone 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 (33.4)	12 (3.4)
Thrombocytopenia[@]	43 (12.2)	22 (6.3)
Anemia[@]	35 (9.9)	20 (5.7)
Leukopenia	14 (4.0)	1 (0.3)
Lymphopenia	10 (2.8)	4 (1.1)
Febrile Neutropenia[%]	8 (2.3)	0 (0.0)
General disorders and administration site conditions		
Fatigue	23 (6.5)	17 (4.9)
Vascular disorders		
Deep vein thrombosis[%]	29 (8.2)	12 (3.4)
Infections and infestations		
Pneumonia[@]	30 (8.5)	19 (5.4)
Urinary Tract Infection	5 (1.4)	1 (0.3)
Metabolism and nutrition disorders		
Hypokalemia	17 (4.8)	5 (1.4)
Hypocalcemia	13 (3.7)	6 (1.7)
Hypophosphatemia	9 (2.5)	0 (0.0)
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism[@]	14 (4.0)	3 (0.9)
Respiratory Distress[@]	4 (1.1)	0 (0.0)
Musculoskeletal and connective tissue disorders		
Muscle weakness	20 (5.7)	10 (2.9)
Gastrointestinal disorders		
Diarrhea[@]	11 (3.1)	4 (1.1)
Constipation	7 (2.0)	1 (0.3)
Nausea[@]	6 (1.7)	2 (0.6)
Cardiac disorders		
Atrial fibrillation[@]	13 (3.7)	4 (1.1)
Tachycardia	6 (1.7)	1 (0.3)
Cardiac Failure Congestive[@]	5 (1.4)	1 (0.3)
Nervous System disorders		
Syncope	10 (2.8)	3 (0.9)
Dizziness	7 (2.0)	3 (0.9)
Eye disorders		
Cataract	6 (1.7)	1 (0.3)
Cataract Unilateral	5 (1.4)	0 (0.0)
Psychiatric Disorder		
Depression	10 (2.8)	6 (1.7)

Table 8: Serious Adverse Reactions Reported in ≥1% Patients and With a ≥1% Difference in Proportion of Patients 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 (1.7)	0 (0.0)
Vascular disorders		
Deep vein thrombosis[%]	26 (7.4)	11 (3.1)
Infections and infestations		
Pneumonia[@]	33 (9.3)	21 (6.0)
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism[@]	13 (3.7)	3 (0.9)
Cardiac disorders		
Atrial fibrillation[@]	11 (3.1)	2 (0.6)
Cardiac Failure Congestive[@]	5 (1.4)	0 (0.0)
Nervous System disorders		
Cerebrovascular accident[@]	(2.0)	3 (0.9)
Gastrointestinal disorders		
Diarrhea[@]	6 (1.7)	2 (0.6)
Musculoskeletal and connective tissue disorders		
Bone Pain	4 (1.1)	0 (0.0)

For 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 (5.3)]
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.

Investigations: blood creatinine increased, hemoglobin decreased, liver functio

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

Musculoskeletal and connective tissue disorders: arthritis, arthritis aggravated

Neoplasms benign, malignant and unspecified: acute leukemia, acute myeloid

Nervous system disorders: cerebrovascular accident, aphasia, cerebellar infa subarachnoid hemorrhage, transient ischemic attack

Psychiatric disorders: confusional state

Renal and urinary disorders: renal failure, hematuria, renal failure acute, azoten

Reproductive system and breast disorders: pelvic pain

Respiratory, thoracic and mediastinal disorders: bronchitis, chronic obstruc infiltration, wheezing

Skin and subcutaneous tissue disorders: acute febrile neutrophilic dermatosis

Vascular system disorders: deep vein thrombosis, hypotension, aortic disorder,

Mantle Cell Lymphoma:
In the MCL trial, a total of 134 patients received at least 1 dose of lenalidomide. 82/134 (61%) had duration of MCL for at least 3 years.

Table 11 summarizes the most frequently observed adverse reactions regardless treatment was 95 days (1-1002 days). Seventy-eight patients (58%) received 3 or cycles. Seventy-six patients (57%) underwent at least one dose interruption d Twenty-six patients (19%) discontinued treatment due to adverse events.

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

Body System Adverse Event	
General disorders and administration site conditions	
Fatigue	
Pyrexia[$]	
Edema peripheral	
Asthenia[$]	
General physical health deterioration	
Gastrointestinal disorders	
Diarrhea[$]	
Nausea[$]	
Constipation	
Vomiting[$]	
Abdominal pain[$]	
Musculoskeletal and connective tissue disorders	
Back pain	
Muscle spasms	
Arthralgia	
Muscular weakness[$]	
Respiratory, thoracic and mediastinal disorders	
Cough	
Dyspnea[$]	
Pleural Effusion	
Hypoxia	
Pulmonary embolism	
Respiratory distress[$]	
Oropharyngeal pain	
Infections and infestations	
Pneumonia[@$]	
Upper respiratory tract infection	
Cellulitis[$]	
Bacteremia[$]	
Staphylococcal sepsis[$]	
Urinary tract infection[$]	
Skin and subcutaneous tissue disorders	
Rash*	
Pruritus	
Blood and lymphatic system disorders	
Neutropenia	
Thrombocytopenia[%$]	
Anemia[$]	
Leukopenia[$]	
Lymphopenia	
Febrile neutropenia[$]	
Metabolism and nutrition disorders	
Decreased appetite	
Hypokalemia	
Dehydration[$]	
Hypocalcemia	
Hyponatremia	
Renal and urinary disorders	
Renal failure[$]	
Vascular disorders	
Hypotension[@$]	
Deep vein thrombosis[$]	
Neoplasms benign, malignant and unspecified (including cysts and p	
Tumor flare	
Squamous cell carcinoma of skin[$]	
Investigations	
Weight decreased	

	PHARMALINE Approval	
nce	Regulatory	Quality Assurance

69 (19.5)	52 (14.9)
61 (17.3)	40 (11.4)
33 (9.3)	15 (4.3)
28 (7.9)	20 (5.7)
25 (7.1)	15 (4.3)

With a ≥1% Difference in Proportion of Patients Between the Lenalidomide/dexmethasone and Placebo/dexametha-

Lenalidomide/Dex* (N=353) n (%)	Placebo/Dex * (N=350) n (%)
118 (33.4)	12 (3.4)
43 (12.2)	22 (6.3)
35 (9.9)	20 (5.7)
14 (4.0)	1 (0.3)
10 (2.8)	4 (1.1)
8 (2.3)	0 (0.0)
23 (6.5)	17 (4.9)
29 (8.2)	12 (3.4)
30 (8.5)	19 (5.4)
5 (1.4)	1 (0.3)
17 (4.8)	5 (1.4)
13 (3.7)	6 (1.7)
9 (2.5)	0 (0.0)
14 (4.0)	3 (0.9)
4 (1.1)	0 (0.0)
20 (5.7)	10 (2.9)
11 (3.1)	4 (1.1)
7 (2.0)	1 (0.3)
6 (1.7)	2 (0.6)
13 (3.7)	4 (1.1)
6 (1.7)	1 (0.3)
5 (1.4)	1 (0.3)
10 (2.8)	3 (0.9)
7 (2.0)	3 (0.9)
6 (1.7)	1 (0.3)
5 (1.4)	0 (0.0)
10 (2.8)	6 (1.7)

and With a ≥1% Difference in Proportion of Patients Between the Lenalidomide/dexamethasone and

Lenalidomide/Dex* (N=353) n (%)	Placebo/Dex* (N=350) n (%)
6 (1.7)	0 (0.0)
26 (7.4)	11 (3.1)
33 (9.3)	21 (6.0)
13 (3.7)	3 (0.9)
11 (3.1)	2 (0.6)
5 (1.4)	0 (0.0)
(2.0)	3 (0.9)
6 (1.7)	2 (0.6)
4 (1.1)	0 (0.0)

reatening (if the outcome of the reaction was death, it is included with death cases)

e/dexamethasone was 44 weeks while median duration of exposure among patients treated with placebo/dexametha-
iparing frequency of adverse reactions between two treatment groups lenalidomide/dexamethasone vs. placebo/dexa-

gs and Precautions (5.3)]
ules.

(8.2%) adverse drug reaction at a higher rate in the lenalidomide/dexamethasone group compared to 3.1 % and 3.4% in
atients with at least 1 prior therapy with discontinuations due to DVT adverse reactions reported at comparable rates
e 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
respectively. Discontinuations and dose reductions due to DVT adverse reactions were reported at comparable rates
Lenalidomide treatment due to DVT adverse reactions was reported at comparable rates between the Rd Continuous

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 43-83) 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 (1-1002 days). Seventy-eight patients (58%) received 3 or more cycles of therapy, 53 patients (40%) received 6 or more cycles, and 26 patients (19%) received 12 or more cycles. Seventy-six patients (57%) underwent at least one dose interruption due to adverse events, and 51 patients (38%) underwent at least one dose reduction due to adverse events. Twenty-six patients (19%) discontinued treatment due to adverse events.

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

Body System Adverse Event	All AEs[1] (N=134) n (%)	Grade 3/4 AEs[2] (N=134) n (%)
General disorders and administration site conditions		
Fatigue	45 (34)	9 (7)
Pyrexia[§]	31 (23)	3 (2)
Edema peripheral	21 (16)	0
Asthenia[§]	19 (14)	4 (3)
General physical health deterioration	3 (2)	2 (1)
Gastrointestinal disorders		
Diarrhea[§]	42 (31)	8 (6)
Nausea[§]	40 (30)	1 (<1)
Constipation	21 (16)	1 (<1)
Vomiting[§]	16 (12)	1 (<1)
Abdominal pain[§]	13 (10)	5 (4)
Musculoskeletal and connective tissue disorders		
Back pain	18 (13)	2 (1)
Muscle spasms	17 (13)	1 (<1)
Arthralgia	11 (8)	2 (1)
Muscular weakness[§]	8 (6)	2 (1)
Respiratory, thoracic and mediastinal disorders		
Cough	38 (28)	1 (<1)
Dyspnea[§]	24 (18)	8 (6)
Pleural Effusion	10 (7)	2 (1)
Hypoxia	3 (2)	2 (1)
Pulmonary embolism	3 (2)	2 (1)
Respiratory distress[§]	2 (1)	2 (1)
Oropharyngeal pain	13 (10)	0
Infections and Infestations		
Pneumonia[¤§]	19 (14)	12 (9)
Upper respiratory tract infection	17 (13)	0
Cellulitis[§]	3 (2)	2 (1)
Bacteremia[§]	2 (1)	2 (1)
Staphylococcal sepsis[§]	2 (1)	2 (1)
Urinary tract infection[§]	5 (4)	2 (1)
Skin and subcutaneous tissue disorders		
Rash*	30 (22)	2 (1)
Pruritus	23 (17)	1 (<1)
Blood and lymphatic system disorders		
Neutropenia	65 (49)	58 (43)
Thrombocytopenia[¤§]	48 (36)	37 (28)
Anemia[§]	41 (31)	15 (11)
Leukopenia[§]	20 (15)	9 (7)
Lymphopenia	10 (7)	5 (4)
Febrile neutropenia[§]	8 (6)	8 (6)
Metabolism and nutrition disorders		
Decreased appetite	19 (14)	1 (<1)
Hypokalemia	17 (13)	3 (2)
Dehydration[§]	10 (7)	4 (3)
Hypocalcemia	4 (3)	2 (1)
Hyponatremia	3 (2)	3 (2)
Renal and urinary disorders		
Renal failure[§]	5 (4)	2 (1)
Vascular disorders		
Hypotension[¤§]	9 (7)	4 (3)
Deep vein thrombosis[§]	5 (4)	5 (4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Tumor flare	13 (10)	0
Squamous cell carcinoma of skin[§]	4 (3)	4 (3)
Investigations		
Weight decreased	17 (13)	0

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% ≥ 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: 0.61-0.85 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 12: Overview of Efficacy Results – Study MM-020 (Intent-to-treat Population)

	Rd Continuous (N = 535)	Rd18 (N = 541)	MPT (N = 547)
PFS – IRAC (months)[a]			
Number of PFS events	278 (52.0)	348 (64.3)	334 (61.1)
Median[a] PFS time, months (95% CI)[b]	25.5 (20.7, 29.4)	20.7 (19.4, 22.0)	21.2 (19.3, 23.2)
HR (95% CI)[c]; p-valued			
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)
Mediana OS time, months (95% CI)[b]	58.9 (56.0, NE)[f]	56.7 (50.1, NE)	48.5 (44.2, 52.0)
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 (%)[a]			
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.

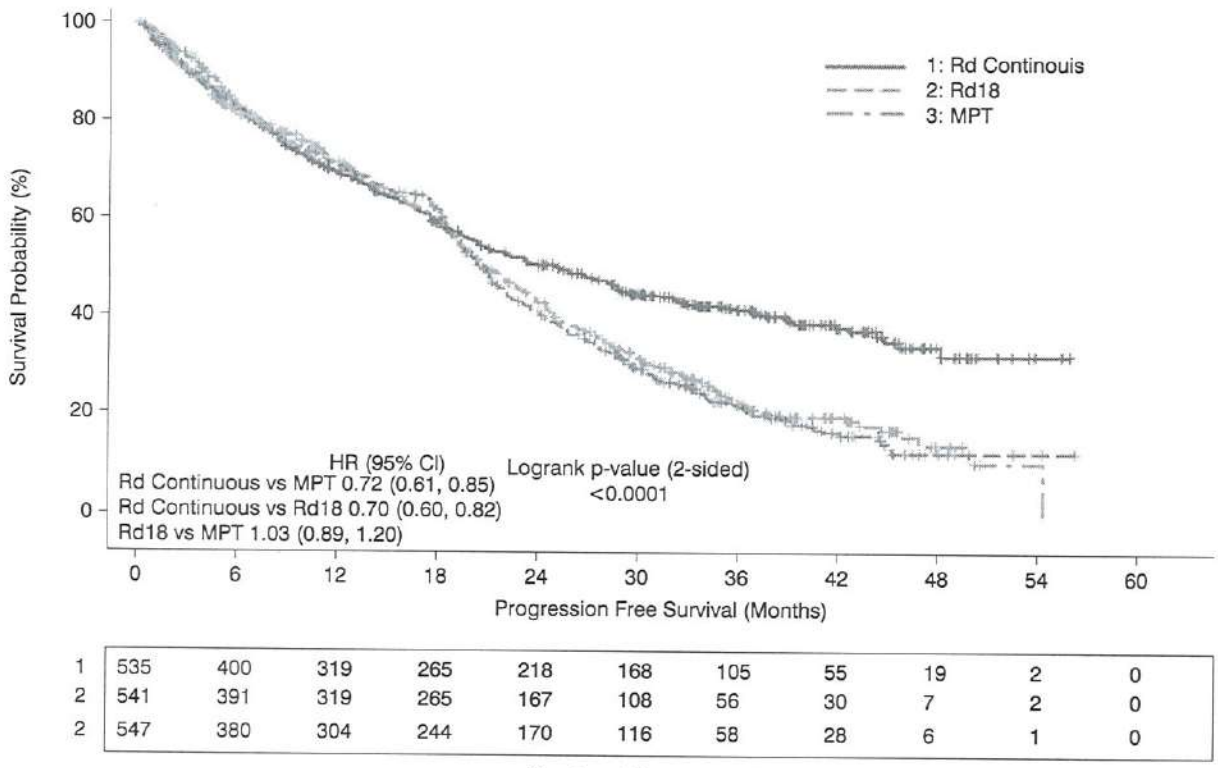
[e]Best assessment of response during the treatment phase of the study

[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 Population) Between Arms Rd Continuous, Rd18 and MPT Cutoff date: 24 May 2013



1	535	400	319	265	218	168	105	55	19	2	0
2	541	391	319	265	167	108	56	30	7	2	0
2	547	380	304	244	170	116	58	28	6	1	0

Number of Subjects at Risk

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

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

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 sca anthracycline or mitoxantrone, cyclophosphamide, rituximab, and bortezomib, alone or in combination. Patients were requi response of PR or better during treatment with bortezomib or a bortezomib-containing regimen), or relapsed disease (defi or a bortezomib-containing regimen). At enrollment patients were to have an absolute neutrophil counts (ANC) ≥1500/ mm³ upper limit of normal (ULN) unless there was documented evidence of liver involvement by lymphoma, serum total bilirubi 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 base in the Mantle Cell Lymphoma trial.

Table 18: Baseline Disease-related Characteristics and Prior Anti–Lymphoma Therapy in Mantle Cell Lymphoma Trial

Baseline Disease Characteristics and Prior Anti-Lymphoma Treatment	
ECOG performance Status[a] n (%) 0 1 2 3	
Advanced MCL Stage, n (%) III IV	
High or Intermediate MIPI Score [b], n (%)	
High Tumor Burden [c], n (%)	
Bulky Disease[d], n (%)	
Extranodal Disease, n (%)	
Number of Prior Systemic Anti-Lymphoma Therapies, n (%) Median (range) 1 2 3 ≥ 4	
Number of Subjects Who Received Prior Regimen Containing, n (%) Anthracycline/mitoxantrone Cyclophosphamide Rituximab Bortezomib	
Refractory to Prior Bortezomib, n (%)	
Refractory to Last Prior Therapy, n (%)	
Prior Autologous Bone Marrow or Stem Cell Transplant, n (%)	

[a] ECOG = Eastern Cooperative Oncology Group

[b] MIPI = MCL International Prognostic Index

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

[d] Bulky disease is defined as at least one lesion that is ≥7cm in the longest diameter

The efficacy endpoints in the MCL trial were overall response rate (ORR) and duration of response (DOR). Response was de review committee according to a modified version of the International Workshop Lymphoma Response Criteria (Cheson, 19 PR) to documented disease progression. The efficacy results for the MCL population were based on all evaluable patients Table 19. The median time to response was 2.2 months (range 1.8 to 13 months).

Table 19: Response Outcomes in the Pivotal Mantle Cell Lymphoma Trial

Response Analyses (N = 133)	**N (%)**
Overall Response Rate (IWRC) (CR + CRu +PR)	34 (26)
Complete Response (CR + CRu)	9 (7)
CR	1 (1)
Cru	8 (6)
Partial Response (PR)	25 (19)
Duration of Response (months)	**Median**
Duration of Overall Response (CR + CRu + PR) (N = 34)	16.6

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

5 mg – Each #2 capsule with white opaque cap and body printed with NAT on cap and 5 mg on body in black ink contains 5 mg bottles of 21

10 mg – Each #2 capsule with white opaque cap and body printed with NAT on cap and 10 mg on body in black ink contair 10 mg bottles of 21

15 mg – Each #2 capsule with white opaque cap and body printed with NAT on cap and 15 mg on body in black ink contair 15 mg bottles of 21

25 mg – Each #2 capsule with white opaque cap and body printed with NAT on cap and 25 mg on body in black ink conta 25 mg bottles of 21

16.2 Storage

Store below 30°C.

16.3 Handling and Disposal

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

Procedures for the proper handling and disposal of anticancer drugs should be considered. Several guidelines on the subj

Dispense no more than a 28-day supply.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the Patient labeling (Medication Guide)

Embryo-Fetal Toxicity

Advise patients that lenalidomide is contraindicated in pregnancy *[see Boxed Warning and Contraindications (4.1)]*. Lenalidc 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 le
- 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 fo simultaneously during lenalidomide capsules therapy, during dose interruption and for 4 weeks after she has completely contraception other than tubal ligation include IUD and hormonal (birth control pills, injections, patch or implants) and a pa 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 pre experiences unusual menstrual bleeding, if she stops taking birth control, or if she thinks FOR ANY REASON that she may
- Advise males to always use a latex or synthetic condom during any sexual contact with females of reproductive potential discontinuing lenalidomide capsules, even if they have undergone a successful vasectomy.
- Advise male patients taking lenalidomide capsules that they must not donate sperm *[see Warnings and Precautions (5.1)*
- All patients must be instructed to not donate blood while taking lenalidomide capsules, during dose interruptions and for *Warnings and Precautions (5.1)]*.

Hematologic Toxicity

Inform patients that lenalidomide is associated with significant neutropenia and thrombocytopenia *[see Boxed Warning an*

Venous and Arterial Thromboembolism

Inform patients of the risk of thrombosis including DVT, PE, MI, and stroke and to report immediately any signs and sympt *and Warning and Precautions (5.3)]*.

greater proportion of patients over 65 years of age discontinued from the clinical studies because of adverse events than the proportion of younger patients (27% vs.16%). No differences in efficacy were observed between patients over 65 years of age and younger patients.

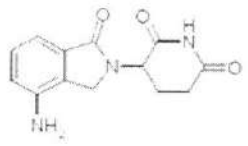
Of the 134 patients with MCL enrolled in the MCL trial, 63% were age 65 and over, while 22% of patients were age 75 and over. The overall frequency of adverse events was similar in patients over 65 years of age and in younger patients (98% vs. 100%). The overall incidence of grade 3 and 4 adverse events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

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

8.6 Renal Impairment
Adjust the starting dose of lenalidomide capsules based on the creatinine clearance value and for patients on dialysis [see Dosage and Administration (2.4)].

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:



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

Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.
Lenalidomide is available in 5 mg, 10 mg, 15 mg and 25 mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: anhydrous lactose. The 5 mg, 10 mg, 15 mg and 25 mg capsule shell contains gelatin and titanium dioxide. Each capsule is printed with black ink, which includes black iron oxide, potassium hydroxide, propylene glycol, and shellac.

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 CK1α) 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, 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 2-sided 90% CI for the mean differences between lenalidomide and placebo was below 10 ms.

12.3 Pharmacokinetics
Absorption
Lenalidomide is rapidly absorbed following oral administration. Following single and multiple doses of 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 Cmax 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 [^{14}C]-lenalidomide binding to plasma proteins is approximately 30%.

Lenalidomide is present in semen at 2 hours (1379 ng/ejaculate) and 24 hours (35 ng/ejaculate) after the administration of 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 (2.4)]*.

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% ≥ 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: 0.61-0.85 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 12: Overview of Efficacy Results – Study MM-020 (Intent-to-treat Population)

	Rd Continuous (N = 535)	Rd18 (N = 541)	MPT (N = 547)
PFS – IRAC (months)[a]			
Number of PFS events	278 (52.0)	348 (64.3)	334 (61.1)
Median[a] PFS time, months (95% CI)[b]	25.5 (20.7, 29.4)	20.7 (19.4, 22.0)	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)		

Hazard Ratio [95% CI]	0.285 [0.210, 0.386]		
Log-rank Test p-value[3]	<0.001		
Response			
Complete Response (CR) n (%)	23 (13)	1 (1)	
Partial Response (RR/PR) n (%)	84 (48)	33 (19)	
Overall Response n (%)	107 (61)	34 (19)	
p-value	<0.001		
Odds Ratio [95% CI]	6.38 [3.95, 10.32]		

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

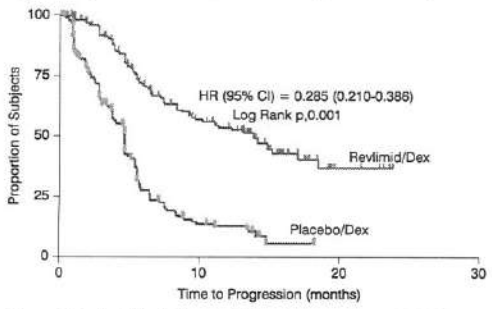
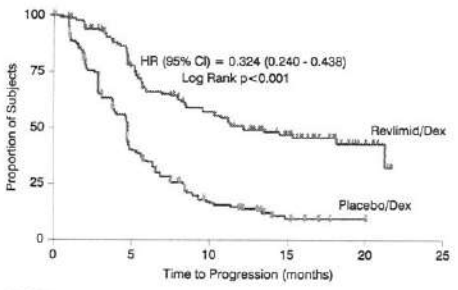


Figure 2: Kaplan-Meier Estimate of Time to Progression — Study 2



14.2 Myelodysplastic Syndromes (MDS) with a Deletion 5q Cytogenetic Abnormality
The efficacy and safety of lenalidomide capsules were evaluated in patients with transfusion-dependent anemia in low-or in isolation or with additional cytogenetic abnormalities, at a dose of 10 mg once daily or 10 mg once daily for 21 days eve study was not designed nor powered to prospectively compare the efficacy of the 2 dosing regimens. Sequential dose delays, were allowed for toxicity *[Dosage and Administration (2.2)]*.

This major study enrolled 148 patients who had RBC transfusion dependent anemia. RBC transfusion dependence was study treatment. The study enrolled patients with absolute neutrophil counts (ANC) ≥ 500/mm³ , platelet counts ≥ 50,000, 3 x upper limit of normal (ULN), and serum direct bilirubin ≤ 2 mg/dL. Granulocyte colony-stimulating factor was permitted neutropenia. Baseline patient and disease-related characteristics are summarized in Table 17.

Table 17: Baseline Demographic and Disease-Related Characteristics in the MDS Study

Age (years)	
Median Min, Max	
Gender	**n**
Male	51
Female	97
Race	**n**
White	143
Other	5
Duration of MDS (years)	
Median Min, Max	
Del 5 (q31-33) Cytogenetic Abnormality	**n**
Yes	148
Other cytogenetic abnormalities	37
IPSS Score[a]	**n**
Low (0)	55
Intermediate -1 (0.5-1.0)	65
Intermediate -2 (1.5-2.0)	6
High(≥ 2.5)	2
Missing	20
FAB Classification[b] from central review	**n**
RA	77
RARS	16
RAEB	30
CMML	3

[a] IPSS Risk Category: Low (combined score = 0), Intermediate-1 (combined score = 0.5 to 1.0), Intermediate-2 (combined score = 1.5 to 2.0), High (combined score >2.5);
Combined score = (Marrow blast score + Karyotype score + Cytopenia score)
[b] French-American-British (FAB) classification of MDS.
The frequency of RBC transfusion independence was assessed using criteria modified from the International Working G was defined as the absence of any RBC transfusion during any consecutive "rolling" 56 days (8 weeks) during the treatm

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

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 1 was 21 days (mean, 35.1 days; range, 2 to 253 days), and the median duration of the first dose interruption was 22 days (interruption due to adverse events was required in 50 (33.8%) of the 148 patients. The median interval between the first days; range, 15 to 205 days) and the median duration of the second dose interruption was 21 days (mean, 26 days; range

14.3 Mantle Cell Lymphoma
A multicenter, single-arm, open-label trial of single-agent lenalidomide was conducted to evaluate the safety and effica relapsed after or were refractory to bortezomib or a bortezomib-containing regimen. Patients with a creatinine clearance for 21 days every 28 days. Patients with a creatinine clearance ≥30 mL/min and <60 mL/min were given lenalidomide at 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 s anthracycline or mitoxantrone, cyclophosphamide, rituximab, and bortezomib, alone or in combination. Patients were req response of PR or better during treatment with bortezomib or a bortezomib-containing regimen), or relapsed disease (de or a bortezomib-containing regimen). At enrollment patients were to have an absolute neutrophil counts (ANC) ≥1500/ mi upper limit of normal (ULN) unless there was documented evidence of liver involvement by lymphoma, serum total biliru 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 bas in the Mantle Cell Lymphoma trial.

Table 18: Baseline Disease-related Characteristics and Prior Anti–Lymphoma Therapy in Mantle Cell Lymphoma Trial

Baseline Disease Characteristics and Prior Anti-Lymphoma Treatment	
ECOG performance Status[a] n (%) 0 1 2 3	
Advanced MCL Stage, n (%) III IV	
High or Intermediate MIPI Score [b], n (%)	
High Tumor Burden [c], n (%)	
Bulky Disease[d], n (%)	
Extranodal Disease, n (%)	
Number of Prior Systemic Anti-Lymphoma Therapies, n (%) Median (range)	

[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
[3]- MCL trial Serious AEs – All treatment-emergent SAEs in 2 or more subjects
[4]- AEs where at least one resulted in a fatal outcome
[5]- AEs where at least one was considered to be Life Threatening (if the outcome of the event was death, it is included with death cases)
[6]- All adverse reactions under Body System of Infections except for rare infections of Public Health Interest will be considered listed
[7]- 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%-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
Musculoskeletal and connective tissue disorders: Pain in extremity
Infections and infestations: Respiratory tract infection, sinusitis, nasopharyngitis, oral herpes
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 (5.7 to 5.10, and 5.12)]*

Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS)
Immune system disorders: Angioedema, acute graft-versus-host disease (following allogeneic hematopoietic transplant), solid organ transplant rejection
Neoplasms benign, malignant and unspecified (incl cysts and polyps): Tumor lysis syndrome, tumor flare reaction
Respiratory, thoracic and mediastinal disorders: Pneumonitis
Hepatobiliary disorders: Hepatic failure (including fatality), toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, mixed cytolytic/cholestatic hepatitis, transient abnormal liver laboratory tests
Infections and infestations: Viral reactivation (such as hepatitis B virus and herpes zoster)
Endocrine disorders: Hypothyroidism, hyperthyroidism

6 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_{tau} were increased by 14%. Periodic monitoring of digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, is recommended during administration of 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 (5.3)].

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
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.
The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. 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 infant, or the effects of lenalidomide capsules on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed infants 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 one 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, during dose interruptions 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.

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 AE categories (eg, all AEs, grade 3/4 AEs, serious AEs) was higher in older (> 75 years of age) than in younger (≤ 75 years of age) subjects. Grade 3 or 4 AEs in the General Disorders and Administration Site Conditions 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 TEAEs in the Infections and Infestations, Cardiac Disorders (including cardiac failure and congestive cardiac failure), Skin and Subcutaneous Tissue Disorders, and Renal and Urinary Disorders (including renal failure) 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 AEs in older vs younger subjects across all treatment arms Serious AEs were generally reported at a higher frequency in the older subjects than in the younger subjects across all treatment arms.

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 ≤ 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 events (100%) was the same in patients over 65 years of age as in younger patients, the frequency of serious adverse events was higher in patients over 65 years of age than in younger patients (54% vs. 33%). A greater proportion of patients over 65 years of age discontinued from the clinical studies because of adverse events than the proportion of younger patients (27% vs.16%). No differences in efficacy were observed between patients over 65 years of age and younger patients.

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

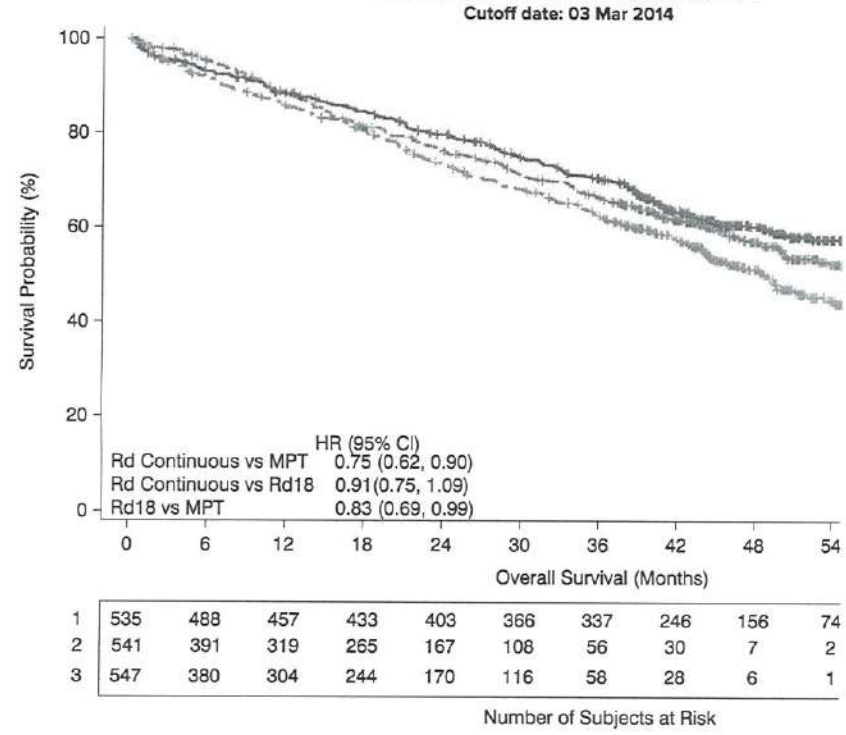
Since elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Monitor renal function.

8.6 Renal Impairment
Adjust the starting dose of lenalidomide capsules based on the creatinine clearance value and for patients on dialysis [see Dosage and Administration (2.4)].

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:

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



1	535	488	457	433	403	366	337	246	156	74
2	541	391	319	265	167	108	56	30	7	2
3	547	380	304	244	170	116	58	28	6	1

Number of Subjects at Risk

OS Events: Rd Continuous=208/535 (38.9%) Rd18=228/541 (42.1%) MPT=261/547

CI = confidence interval; d = low-dose dexamethasone; HR = hazard ratio; M = melphalan; P = prednisone; R = lenalidomide; Rd C 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 multicente compared lenalidomide plus oral pulse high-dose dexamethasone therapy to dexamethasone therapy alone in patients with MM wh enrolled patients with absolute neutrophil counts (ANC) ≥ 1000/mm³, platelet counts ≥ 75,000/mm³, serum creatinine ≤ 2.5 mg/dL, s (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 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. Pat sone 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 disease progression.
In both studies, dose adjustments were allowed based on clinical and laboratory findings. Sequential dose reductions to 15 mg daily, Dosage and Administration (2.1)].
Table 15 summarizes the baseline patient and disease characteristics in the two studies. In both studies, baseline demographic and c the lenalidomide /dexamethasone and placebo/dexamethasone groups.

Table 15: Baseline Demographic and Disease-Related Characteristics – Studies 1 and 2

	Study 1		
	Lenalidomide /Dex N=177	**Placebo/Dex N=176**	**Lenalidomide / N=176**
Patient Characteristics			
Age (years) Median Min, Max	64 36, 86	62 37, 85	63 33, 84
Sex Male Female	106 (60%) 71 (40%)	104 (59%) 72 (41%)	104 (59% 72 (41%
Race/Ethnicity White Other	141(80%) 36 (20%)	148 (84%) 28 (16%)	172 (98% 4 (2%)
ECOG Performance Status 0-1	157 (89%)	168 (95%)	150 (85%
Disease Characteristics			
Multiple Myeloma Stage (Durie-Salmon) I II III	3% 32% 64%	3% 31% 66%	6% 28% 65%
β2-microglobulin (mg/L) ≤ 2.5 mg/L > 2.5 mg/L	52 (29%) 125 (71%)	51 (29%) 125 (71%)	51 (29%) 125 (71%
Number of Prior Therapies			
1 ≥ 2	38% 62%	38% 62%	32% 68%
Types of Prior Therapies			
Stem Cell Transplantation	62%	61%	55%
Thalidomide	42%	46%	30%
Dexamethasone	81%	71%	66%
Bortezomib	11%	11%	5%
Melphalan	33%	31%	56%
Doxorubicin	55%	51%	56%

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

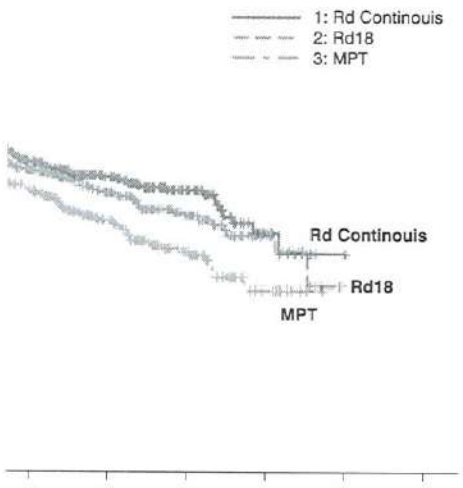
Preplanned interim analyses of both studies showed that the combination of lenalidomide /dexamethasone was significantly supe unblinded to allow patients in the placebo/dexamethasone group to receive treatment with the lenalidomide/dexamethasone comt data with crossovers were analyzed. In study 1, the median survival time was 39.4 months (95%CI: 32.9, 47.4) in lenalidomide/dexa placebo/dexamethasone group, with a hazard ratio of 0.79 (95% CI: 0.61-1.03). In study 2, the median survival time was 37.5 months and 30.8 months (95%CI: 23.5, 40.3) in placebo/dexamethasone group, with a hazard ratio of 0.86 (95% CI: 0.65-1.14).

Table 16: TTP Results in Study 1 and Study 2

	Study 1		
	Lenalidomide /Dex N=177	**Placebo/Dex N=176**	**Lenalidomide N=176**
TTP			
Events n (%)	73 (41)	120 (68)	68 (39)
Median TTP in months [95% CI]	**13.9** [9.5, **18.5**]	4.7 [3.7, 4.9]	12.1 [9.5, NE]
Hazard Ratio [95% CI]	0.285 [0.210, 0.386]		
Log-rank Test p-value[3]	<0.001		
Response			
Complete Response (CR) n (%)	23 (13)	1 (1)	27 (15
Partial Response (RR/PR) n (%)	84 (48)	33 (19)	77 (44
Overall Response n (%)	107 (61)	34 (19)	104 (5
p-value	<0.001		
Odds Ratio [95% CI]	6.38 [3.95, 10.32]		

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

al (ITT Population)
f18 and MPT
14



28/541 (42.1%) MPT=261/547 (47.7%)

sone; R = lenalidomide; Rd Continuous = Rd given until documentation of progressive

nalidomide. These multicenter, multinational, double-blind, placebo-controlled studies alone in patients with MM who had received at least one prior treatment. These studies rum creatinine ≤ 2.5 mg/dL, serum SGOT/AST or SGPT/ALT ≤ 3 x upper limit of normal

once daily on Days 1 to 21 and a matching placebo capsule once daily on Days 22 to 28 o 28 of each 28-day cycle. Patients in both treatment groups took 40 mg of dexametha- therapy.
cycle after the first 4 cycles of therapy. In both studies, treatment was to continue until

ose reductions to 15 mg daily, 10 mg daily and 5 mg daily were allowed for toxicity [see

, baseline demographic and disease-related characteristics were comparable between

	Study 2	
	Lenalidomide /Dex N=176	Placebo/Dex N=175
	63 33, 84	64 40, 82
	104 (59%) 72 (41%)	103 (59%) 72 (41%)
	172 (98%) 4 (2%)	175(100%) 0 (0%)
	150 (85%)	144 (82%)
	6% 28% 65%	5% 33% 63%
	51 (29%) 125 (71%)	48 (27%) 127 (73%)
	32% 68%	33% 67%
	55%	54%
	30%	38%
	66%	69%
	5%	4%
	56%	52%
	56%	57%

me from randomization to the first occurrence of progressive disease.

hasone was significantly superior to dexamethasone alone for TTP. The studies were lomide/dexamethasone combination. For both studies, the extended follow-up survival 2.9, 47.4) in lenalidomide/dexamethasone group and 31.6 months (95%CI: 24.1, 40.9) in urvival time was 37.5 months (95%CI: 29.9, 46.6) in lenalidomide/dexamethasone group % CI: 0.65-1.14).

	Study 2	
	Lenalidomide /Dex N=176	Placebo/Dex N=175
	68 (39)	130 (74)
	12.1 [9.5, NE]	4.7 [3.8, 4.8]
	0.324 [0.240, 0.438]	
	<0.001	
	27 (15)	7 (4)
	77 (44)	34 (19)
	104 (59)	41 (23)
	<0.001	
	4.72 [2.98, 7.49]	

Increased Mortality in Patients with CLL
Inform patients that lenalidomide had increased mortality in patients with CLL and serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure *[see Warning and Precautions (5.4)]*.

Second Primary Malignancies
Inform patients of the potential risk of developing second primary malignancies during treatment with Lenalidomide *[see Warnings and Precautions (5.5)]*.

Hepatotoxicity
Inform patients of the risk of hepatotoxicity, including hepatic failure and death, and to report any signs and symptoms associated with this event to their healthcare provider for evaluation [see Warnings and Precautions (5.7)].

Severe Cutaneous Reactions Including Hypersensitivity Reactions
Inform patients of the potential for severe reactions including hypersensitivity, angioedema, Stevens-Johnson Syndrome, toxic epidermal necrolysis or drug reaction with eosinophilia and systemic symptoms if they had such a reaction to thalidomide and report symptoms associated with these events to their healthcare provider for evaluation *[see Warnings and Precautions (5.8)]*.

Tumor Lysis Syndrome
Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions (5.9)]*.

Tumor Flare Reaction
Inform patients of the potential risk of tumor flare reaction and to report any signs and symptoms associated with this event to their healthcare provider for evaluation [see Warnings and Precautions (5.10)].

Early Mortality in Patients with MCL
Inform patients with MCL of the potential for early death *[see Warnings and Precautions (5.13)]*.
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.

Packed by:
Pharmaline - Lebanon
Liscenced By:
Natco Pharma Limited, India

Revised: 5/2018

MEDICATION GUIDE
LENALIDOMIDE (len" a lid' oh mide) Capsules
What is the most important information I should know about lenalidomide capsules?
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:
o For at least 4 weeks before starting lenalidomide capsules
o While taking lenalidomide capsules
o During any breaks (interruptions) in your treatment with lenalidomide capsules
o For at least 4 weeks after stopping lenalidomide capsules
Females who can become pregnant:
o 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.
o If you miss your period or have unusual bleeding, you will need to have a pregnancy test and receive counseling.
o 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 capsuleslenalidomide capsules.
o 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.
o 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.
Lenalidomide can pass into human semen:
o 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 who 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.
o 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.
o Do not donate sperm while taking lenalidomide capsules, during any breaks (interruptions) in your treatment, and for 4 weeks after stopping lenalidomide capsules. If a female becomes pregnant with your sperm, the baby may be exposed to Lenalidomide capsules 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 causes low white blood cells and low platelets in most people. You may need a blood transfusion or certain medicines if your blood counts drop too low. Your healthcare provider should check your blood counts often especially during the first several months of treatment with lenalidomide, 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:
o If you have had a blood clot in the past
o If you have high blood pressure, smoke, or if you have been told that you have a high level of fat in your blood (hyperlipidemia)
o About all the medicines you take. Certain other medicines can also increase your risk for blood clots.

Call your healthcare provider or get medical help right away if you get any of the following during treatment with lenalidomide:

o **Signs or symptoms of a blood clot in the lung, arm, or leg may include:** shortness of breath, chest pain, or arm or leg swelling
o **Signs or symptoms of a heart attack may include:** chest pain that may spread to the arms, neck, jaw, back, or stomach area (abdomen), feeling sweaty, shortness of breath, feeling sick or vomiting
o **Signs or symptoms of stroke may include:** sudden numbness or weakness, especially on one side of the body, severe headache or confusion, or problems with vision, speech, or balance.
What are lenalidomide capsules?
Lenalidomide is a prescription medicine used to treat people with:
• multiple myeloma (MM)
o in combination with the medicine dexamethasone, or
• 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 two 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 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
• 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.
o If powder from the lenalidomide capsules comes in contact with your skin, wash the skin right away with soap and water.
o If powder from the lenalidomide capsules 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 capsules or overdose, 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.**
• **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 capsules and may be born with birth defects.
What are the possible side effects of lenalidomide capsules?
Lenalidomide capsules may 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:
o yellowing of your skin or the white part of your eyes (jaundice)
o dark or brown (tea- colored) urine
o pain on the upper right side of your stomach area (abdomen)
o bleeding or bruising more easily than normal
o feeling very tired

• **Severe skin reactions including severe allergic reactions** can happen with lenalidomide capsules and may cause death. Call your healthcare provider right away if you develop any of these signs or symptoms of a severe allergic reaction or severe skin reaction during treatment with lenalidomide capsules.
o swelling of your face, eyes, lips, tongue, throat
o trouble swallowing
o trouble breathing
o skin rash, hives, or peeling of your skin
o blisters
o rash with fever and or swollen glands
• **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

ıath cases)
l listed

ed above have been reported (1%-10%) in patients treated with

onotherapy for mantle cell lymphoma.

capsules. Because these reactions are reported voluntarily from
to drug exposure *[see Warnings and Precautions Section (5.7 to*

phillia and systemic symptoms (DRESS)
id organ transplant rejection

ytic/cholestatic hepatitis, transient abnormal liver laboratory tests

e increased by 14%. Periodic monitoring of digoxin plasma levels,
ended during administration of lenalidomide capsules.

id be used with caution after making a benefit-risk assessment in

ct on the pharmacokinetics of lenalidomide or R-and S-warfarin.
re not affected by concomitant lenalidomide capsules administra-
recommended in patients with MM taking concomitant warfarin.

e can cause embryo-fetal harm when administered to a pregnant
(5.1)].

fe-threatening birth defects such as amelia (absence of limbs),
pinna, small or absent external auditory canals), facial palsy, eye
rmations have also been documented and mortality at or shortly

ition to pregnant rabbits and pregnant rats [see Data]. If this drug
tential risk to a fetus.

bstetrician/gynecologist experienced in reproductive toxicity for

ed background risk in the U.S. general population of major birth

in offspring when pregnant monkeys received oral lenalidomide
recommended human dose (MRHD) of 25 mg. Similar studies in
erse reproductive effects in rats.

study revealed a few adverse effects on the offspring of female
urface area). The male offspring exhibited slightly delayed sexual
th thalidomide, the rat model may not adequately address the full

asma lenalidomide concentrations were approximately 20 to 40%
ıncentrations of radioactivity in fetal tissues were generally lower

breastfed infant, or the effects of lenalidomide capsules on milk
stfed infants from lenalidomide capsules, advise women not to

fy the pregnancy status of females of reproductive potential prior
id pregnancy 4 weeks before therapy, while taking lenalidomide

st should be performed within 10 to 14 days, and the second test
nancy testing for females of reproductive potential should occur
nenstrual cycles. If menstrual cycles are irregular, the pregnancy
f there is any abnormality in her menstrual bleeding. Lenalidomide

se 2 methods of reliable birth control simultaneously: one highly
or implants), or partner's vasectomy, and one additional effective
to initiating treatment with lenalidomide capsules, during therapy.
on is indicated even where there has been a history of infertility,
thods, if needed.

or synthetic condom during any sexual contact with females of
lenalidomide capsules, even if they have undergone a successful

years of age or older, while 35% (561/1613) were over 75 years of
verall, across all treatment arms, the frequency in most of the AE
bjects. Grade 3 or 4 AEs in the General Disorders and Administra-
bjects than in younger subjects across all treatment arms. Grade
Skin and Subcutaneous Tissue Disorders, and Renal and Urinary
e), in older subjects than in younger subjects across all treatment
scular Disorders), there was a less consistent trend for increased
gher frequency in the older subjects than in the younger subjects

age 65 or over while 12% of patients were age 75 and over. The
ebo/dexamethasone groups. Of the 353 patients who received
tients ≤ 65 years of age to experience DVT, pulmonary embolism,
patients over 65 years of age and younger patients.

Although the overall frequency of adverse events (100%) was the
s over 65 years of age than in younger patients (54% vs. 33%). A
ıe proportion of younger patients (27% vs.16%). No differences in

r. The overall frequency of adverse events was similar in patients
similar in these 2 patient groups (79% vs. 78%, respectively). The
differences in efficacy were observed between patients over 65

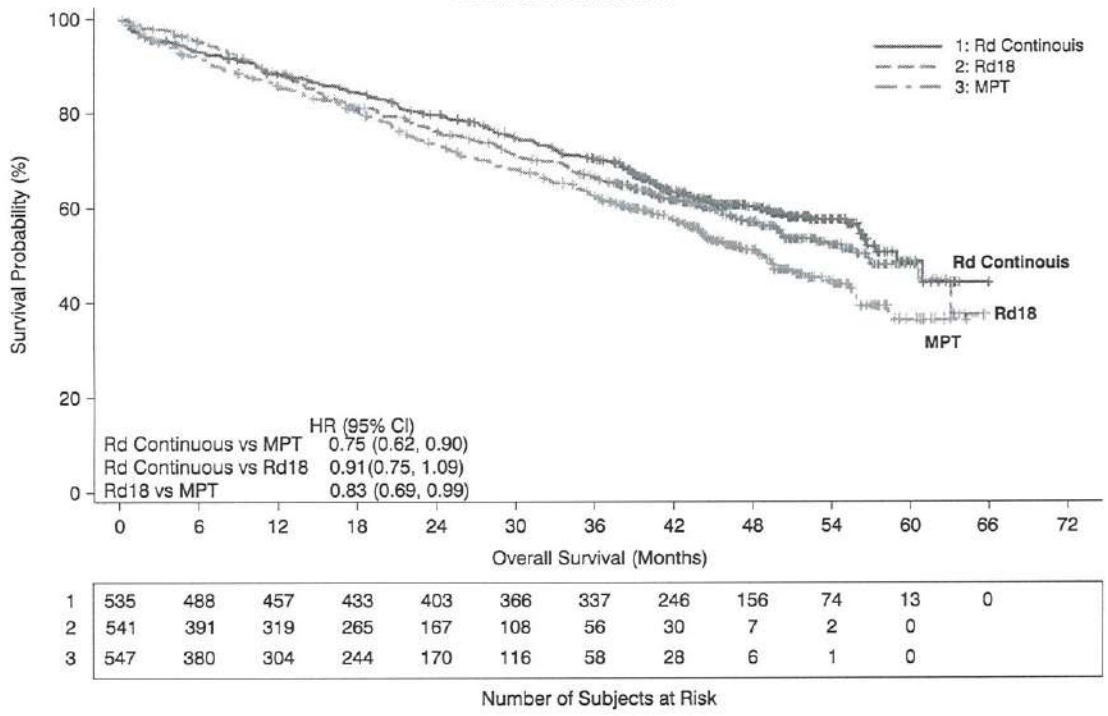
l function.

osage and Administration (2.4)].

jing studies in healthy subjects, some were exposed to up to 200
ash, and elevated liver transaminases were the primary reported

e chemical name is 3- (4-amino-1-oxo 1,3-dihydro-2H-isoindol-2-yl)

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



OS Events: Rd Continuous=208/535 (38.9%) Rd18=228/541 (42.1%) MPT=261/547 (47.7%)

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) ≥ 1000/mm³, platelet counts ≥ 75,000/mm³, 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 15 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 15: Baseline Demographic and Disease-Related Characteristics – 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 Min, Max	64 36, 86	62 37, 85	63 33, 84	64 40, 82
Sex Male Female	106 (60%) 71 (40%)	104 (59%) 72 (41%)	104 (59%) 72 (41%)	103 (59%) 72 (41%)
Race/Ethnicity White Other	141(80%) 36 (20%)	148 (84%) 28 (16%)	172 (98%) 4 (2%)	175(100%) 0 (0%)
ECOG Performance Status 0-1	157 (89%)	168 (95%)	150 (85%)	144 (82%)
Disease Characteristics				
Multiple Myeloma Stage (Durie-Salmon) I II III	3% 32% 64%	3% 31% 66%	6% 28% 65%	5% 33% 63%
β2-microglobulin (mg/L) ≤ 2.5 mg/L > 2.5 mg/L	52 (29%) 125 (71%)	51 (29%) 125 (71%)	51 (29%) 125 (71%)	48 (27%) 127 (73%)
Number of Prior Therapies				
1 ≥ 2	38% 62%	38% 62%	32% 68%	33% 67%
Types of Prior Therapies				
Stem Cell Transplantation	62%	61%	55%	54%
Thalidomide	42%	46%	30%	38%
Dexamethasone	81%	71%	66%	69%
Bortezomib	11%	11%	5%	4%
Melphalan	33%	31%	56%	52%
Doxorubicin	55%	51%	56%	57%

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

Preplanned interim analyses of both studies showed that the combination of 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: 0.61-1.03). 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: 0.65-1.14).

Table 16: TTP Results in 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[a]	<0.001		<0.001	
Response				
Complete Response (CR) n (%)	23 (13)	1 (1)	27 (15)	7 (4)
Partial Response (RR/PR) n (%)	84 (48)	33 (19)	77 (44)	34 (19)
Overall Response n (%)	107 (61)	34 (19)	104 (59)	41 (23)
p-value	<0.001		<0.001	
Odds Ratio [95% CI]	6.38 [3.95, 10.32]		4.72 [2.98, 7.49]	

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

Increased Mortality in Patients with CLL
Inform patients that lenalidomide had increased mortality in patients wit
failure *[see Warning and Precautions (5.4)].*

Second Primary Malignancies
Inform patients of the potential risk of developing second primary malign

Hepatotoxicity
Inform patients of the risk of hepatotoxicity, including hepatic failure and
[see Warnings and Precautions (5.7)].

Severe Cutaneous Reactions Including Hypersensitivity Reactions
Inform patients of the potential for severe reactions including hypersens
systemic symptoms if they had such a reaction to thalidomide and report
(5.8)].

Tumor Lysis Syndrome
Inform patients of the potential risk of tumor lysis syndrome and to repor
Precautions (5.9)].

Tumor Flare Reaction
Inform patients of the potential risk of tumor flare reaction and to report
Precautions (5.10)].

Early Mortality in Patients with MCL
Inform patients with MCL of the potential for early death *[see Warnings ar*
Dosing Instructions
Inform patients how to take lenalidomide capsules *[see Dosage and Adm*
• Lenalidomide capsules should be taken once daily at about the same tir
• Lenalidomide capsules may be taken either with or without food.
• The capsules should not be opened, broken, or chewed. Lenalidomide
• Instruct patients that if they miss a dose of lenalidomide capsules, they
should be instructed to skip the dose for that day. The next day, they shou
missed.

Packed by:
Pharmaline - Lebanon
Liscenced By:
Natco Pharma Limited, India

Revised: 5/2018

MEDICATION GUIDE
LENALIDOMIDE (len" a lid' oh mide) Capsules
What is the most important information I should know about lenalidom
Lenalidomide capsules may cause serious side effects including:
• **Possible birth defects (deformed babies) or death of an unborn baby. Lenalidomide is similar to the medicine thalidomide.** We know thalidomi
Lenalidomide capsules have harmed unborn animals in animal testing.
Females must not get pregnant:
o For at least 4 weeks before starting lenalidomide capsules
o While taking lenalidomide capsules
o During any breaks (interruptions) in your treatment with lenalidomide ca
o For at least 4 weeks after stopping lenalidomide capsules
Females who can become pregnant:
o Will have pregnancy tests weekly for 4 weeks, then every 4 weeks if yo
o If you miss your period or have unusual bleeding, you will need to have
o Must agree to use two acceptable forms of birth control at the same ti
weeks after stopping lenalidomide capsuleslenalidomide capsules.
o Talk with your healthcare provider to find out about options for acceptab
capsules.
o If you had unprotected sex or if you think your birth control has failed, s
If you become pregnant while taking lenalidomide capsules, stop takin
Lenalidomide can pass into human semen:
o Males, including those who have had a vasectomy, must always use a l
while taking lenalidomide capsules, during any breaks (interruptions) in yo
o Do not have unprotected sexual contact with a female who is or could
could become pregnant.
o Do not donate sperm while taking lenalidomide capsules, during any b
pregnant with your sperm, the baby may be exposed to Lenalidomide cap

Men, if your female partner becomes pregnant, you should call your he
• **Low white blood cells (neutropenia) and low platelets (thrombocytope** transfusion or certain medicines if your blood counts drop too low. Your he lenalidomide, and then at least monthly. Tell your healthcare provider if yo
• **Blood clots.** Blood clots in the arteries, veins, and lungs happen more o the medicine dexamethasone with Lenalidomide capsules. Heart attacks increased risk, most people who take lenalidomide capsules will also take

Before taking Lenalidomide capsules, tell your healthcare provider:
o If you have had a blood clot in the past
o If you have high blood pressure, smoke, or if you have been told that yo
o About all the medicines you take. Certain other medicines can also incr

Call your healthcare provider or get medical help right away if you get an

o **Signs or symptoms of a blood clot in the lung, arm, or leg may includ**
o **Signs or symptoms of a heart attack may include:** chest pain that may vomiting
o **Signs or symptoms of stroke may include:** sudden numbness or weakn
What are lenalidomide capsules?
Lenalidomide is a prescription medicine used to treat people with:
• multiple myeloma (MM)
o in combination with the medicine dexamethasone, or
• a condition called myelodysplastic syndromes (MDS). Lenalidomide caps is known as deletion 5q MDS. People with this type of MDS may have low
• mantle cell lymphoma (MCL) when the disease comes back or becomes blood cell called lymphocytes that are in the lymph nodes.
Lenalidomide should not be used to treat people who have chronic lymph 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** durir **lenalidomide capsules?"**
• are allergic to lenalidomide or any of the ingredients in lenalidomide cap
What should I tell my healthcare provider before taking lenalidomide c
Before you take lenalidomide capsules, tell your healthcare provider **abou**
• 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
• are lactose intolerant. Lenalidomide capsules contain lactose.
• are breastfeeding. Do not breastfeed during treatment with lenalidomid
Tell your healthcare provider about all the medicines you take, including medicines may affect each other causing serious side effects. Talk with yo Know the medicines you take. Keep a list of them to show your healthcar
How should I take lenalidomide capsules?
Take lenalidomide capsules exactly as prescribed
• Swallow lenalidomide capsules whole with water 1 time a day. **Do not op**
• **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 t
o If powder from the lenalidomide capsules comes in contact with your sk
o If powder from the lenalidomide capsules comes in contact with the ins
• If you miss a dose of lenalidomide capsules, and it has been less than 1 missed dose. Do **not** take 2 doses at the same time.
• If you take too much lenalidomide capsules or overdose, call your healt
What should I avoid while taking lenalidomide capsules?
• See "What is the most important information I should know about lenalic
• **Females: Do not get pregnant and do not breastfeed while taking len**
• **Males: Do not donate sperm.**
• **Do not share lenalidomide capsules with other people.** It may cause b
• **Do not donate blood** while you take lenalidomide capsules, during any pregnant gets your donated blood, her baby may be exposed to lenalido
What are the possible side effects of lenalidomide capsules?
Lenalidomide capsules may cause serious side effects, including:
• See "What is the most important information I should know about lenalic
• **Increased risk of death in people who have chronic lymphocytic leuke** who take the medicine chlorambucil. Lenalidomide capsules may cause You should not take lenalidomide capsules if you have CLL unless you ar
• **Risk of new cancers (malignancies).** An increase in new (second) canc including certain blood cancers, such as acute myelogenous leukemia (Al your healthcare provider about your risk of developing new cancers if yo lenalidomide capsules.
• **Severe liver problems, including liver failure and death.** Your healthcar your healthcare provider right away if you develop any of the following sy
o yellowing of your skin or the white part of your eyes (jaundice)
o dark or brown (tea- colored) urine
o pain on the upper right side of your stomach area (abdomen)
o bleeding or bruising more easily than normal
o feeling very tired

• **Severe skin reactions including severe allergic reactions** can happen w signs or symptoms of a severe allergic reaction or severe skin reaction di
o swelling of your face, eyes, lips, tongue, throat
o trouble swallowing
o trouble breathing
o skin rash, hives, or peeling of your skin
o blisters
o rash with fever and or swollen glands
• **Tumor lysis syndrome (TLS).** TLS is caused by the fast breakdown of c

rs of age than in younger patients (54% vs. 33%). A
of younger patients (27% vs.16%). No differences in

frequency of adverse events was similar in patients
se 2 patient groups (79% vs. 78%, respectively). The
efficacy were observed between patients over 65

ministration (2.4)].

healthy subjects, some were exposed to up to 200
ated liver transaminases were the primary reported

ne is 3- (4-amino-1-oxo 1,3-dihydro-2H-isoindol-2-yl)

nalidomide is more soluble in organic solvents and
ric carbon atom and can exist as the optically active

ve ingredient and the following inactive ingredients:
ack ink, which includes black iron oxide, potassium

alidomide are mediated through its target cereblon,
aros, and CK1α) are targeted for ubiquitination and
osis of certain hematopoietic tumor cells including
ic tumor models including MM. Immunomodulatory
ibody-dependent cell-mediated cytotoxicity (ADCC)
es (e.g., TNF-α and IL-6) by monocytes.In MM cells,

naximum recommended dose, lenalidomide did not
below 10 ms.

h MM or MDS the maximum plasma concentrations
nd Cmax values increasing proportionally with dose.

with an approximate 20% decrease in AUC and 50%
t regard to food intake. Lenalidomide capsules can

mg daily.

tified metabolites are 5-hydroxy-lenalidomide and

d 4% of the radioactive dose was eliminated within
ours. Hydroxy-lenalidomide and N-acetyl-lenalido-
rate.

), 9 subjects with moderate renal impairment (CLcr
dialysis were administered a single 25 mg dose of
gle 25 mg dose of lenalidomide capsules. As CLcr
se in half-life and a 66% to 75% decrease in drug
se in drug clearance compared to healthy subjects.

on (2.4)].

greater than ULN) did not influence the disposition

or MCL) did not have a clinically relevant effect on

nacokinetics of lenalidomide (25 mg).
nificantly increase the C_{max} or AUC of lenalidomide.

pharmacokinetics of lenalidomide, temsirolimus, or

cer resistance protein (BCRP), multidrug resistance
de 1B1 (OATP1B1), organic cation transporters (OCT)
alidomide is not an inhibitor of P-gp, bile salt export

halidomide does not inhibit bilirubin glucuronidation

human peripheral blood lymphocytes, or mutations
Hamster Embryo assay or induce micronuclei in the

human dose of 25 mg, based on body surface area)

low-dose dexamethasone (Rd) given for 2 different
stem cell transplant. In the first arm of the study, Rd
[72 weeks, Arm Rd18]). In the third arm, melphalan,
who was < 65 years of age was not a candidate for
stratified at randomization by age (≤75 versus >75

as dosed 40 mg once daily on Days 1, 8, 15, and 22
and 22 of repeated 28-day cycles. Initial dose and
n with the most commonly used being aspirin.
cts had advanced-stage disease. Of the total study
% had severe renal impairment (creatinine clearance
For ECOG Performance Status, 29% were Grade 0,

isease progression as determined by Independent
never occurred first during the study until the end of
efficacy results are summarized in the table below.
d Continuous arm compared with the MPT arm had
4.3 months. The myeloma response rate was higher
% in the MPT arm. The median time to first response

ith events, representing 78% of prespecified events
95% CI = 0.62, 0.90).

	MPT (N = 547)
	334 (61.1)
	21.2 (19.3, 23.2)

Hazard Ratio [95% CI]	0.285 [0.210, 0.386]		0.324 [0.240, 0.438]	
Log-rank Test p-value[3]	<0.001		<0.001	
Response				
Complete Response (CR) n (%)	23 (13)	1 (1)	27 (15)	7 (4)
Partial Response (RR/PR) n (%)	84 (48)	33 (19)	77 (44)	34 (19)
Overall Response n (%)	107 (61)	34 (19)	104 (59)	41 (23)
p-value	<0.001		<0.001	
Odds Ratio [95% CI]	6.38 [3.95, 10.32]		4.72 [2.98, 7.49]	

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

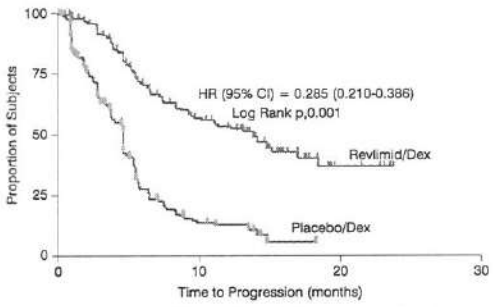
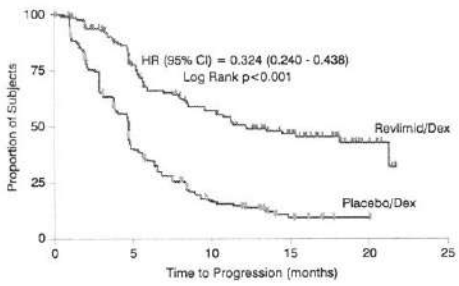


Figure 2: Kaplan-Meier Estimate of Time to Progression — Study 2



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

The efficacy and safety of 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 *[Dosage and Administration (2.2)]*.

This major study enrolled 148 patients who had RBC transfusion dependent anemia. RBC transfusion dependence was defined as having received ≥ 2 units of RBCs within 8 weeks prior to study treatment. The study enrolled patients with absolute neutrophil counts (ANC) ≥ 500/mm³ , platelet counts ≥ 50,000/mm³, serum creatinine ≤ 2.5 mg/dL, serum SGOT/AST or SGPT/ALT ≤ 3 x upper limit of normal (ULN), and serum direct bilirubin ≤ 2 mg/dL. Granulocyte colony-stimulating factor was permitted for patients who developed neutropenia or fever in association with neutropenia. Baseline patient and disease-related characteristics are summarized in Table 17.

Table 17: Baseline Demographic and Disease-Related Characteristics in the MDS Study

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

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

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

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

RBC transfusion independence rates were unaffected by age or gender.

The dose of 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) ≥1500/ mm³, platelet counts ≥ 60,000/mm³, serum SGOT/AST or SGPT/ALT ≤3x upper limit of normal (ULN) unless there was documented evidence of liver involvement by lymphoma, serum total bilirubin ≤1.5 x ULN except in cases of Gilbert's syndrome or documented liver involvement by lymphoma, and calculated creatinine clearance (Cockcroft-Gault formula) ≥30 mL/min.

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

Table 18: 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 1 2 3	 43 (32) 73 (54) 17 (13) 1 (<1)
Advanced MCL Stage, n (%) III IV	 27 (20) 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 (%)	

• Increased risk of death in people who have chronic lymphocytic leukemia (CLL). Pe
who take the medicine chlorambucil. Lenalidomide capsules may cause you to have s
You should not take lenalidomide capsules if you have CLL unless you are participating
• Risk of new cancers (malignancies). An increase in new (second) cancers has happ
including certain blood cancers, such as acute myelogenous leukemia (AML), and myel
your healthcare provider about your risk of developing new cancers if you take lenalid
lenalidomide capsules.
• Severe liver problems, including liver failure and death. Your healthcare provider sh
your healthcare provider right away if you develop any of the following symptoms of liv
o yellowing of your skin or the white part of your eyes (jaundice)
o dark or brown (tea- colored) urine
o pain on the upper right side of your stomach area (abdomen)
o bleeding or bruising more easily than normal
o feeling very tired

• Severe skin reactions including severe allergic reactions can happen with lenalidomi
signs or symptoms of a severe allergic reaction or severe skin reaction during treatmen
o swelling of your face, eyes, lips, tongue, throat
o trouble swallowing
o trouble breathing
o skin rash, hives, or peeling of your skin
o blisters
o rash with fever and or swollen glands
• Tumor lysis syndrome (TLS). TLS is caused by the fast breakdown of cancer cells. T
sometimes death. Your healthcare provider may do blood tests to check you for TLS.
• Worsening of your tumor (tumor flare reaction). Tell your healthcare provider if you
lymph nodes, low grade fever, pain, or rash.
Your healthcare provider may tell you to decrease your dose, temporarily stop or perm
with lenalidomide capsules.
• Thyroid problems. Your healthcare provider may check your thyroid function before y
• Risk of Early Death in MCL. In people who have Mantle Cell Lymphoma (MCL), there m
provider about any concerns and possible risk factors.
The most common side effects of lenalidomide capsules include:
• diarrhea
• constipation
• itching
• rash
• tiredness
• swelling of the limbs and skin
• nausea
• fever
• cough

These are not all the possible side effects of lenalidomide capsules.
Call your doctor for medical advice about side effects.
How should I store lenalidomide capsules?
• Store lenalidomide capsules below 30°C.
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 Medicatic
give lenalidomide capsules to other people, even if they have the same symptoms you
If you would like more information, talk with your healthcare provider. You can ask your h
professionals.
What are the ingredients in lenalidomide capsules?
Active ingredient: lenalidomide
Inactive ingredients: anhydrous lactose.
The 5 mg, 10 mg, 15 mg and 25 mg capsule shell contains gelatin and titanium dioxide.
Each capsule is printed with black ink, which includes black iron oxide, potassium hydr

Manufactured by
Natco Pharma Limited Kothur-509228
Rangareddy District Telangana, India

Packed by:
Pharmaline - Lebanon
Liscensed by:
Natco Pharma Limited, India

Revised: 11/2018

0.324 [0.240, 0.438]	
<0.001	
5)	7 (4)
14)	34 (19)
(59)	41 (23)
<0.001	
4.72 [2.98, 7.49]	

late-1-risk MDS with a 5q (q31 to 33) cytogenetic abnormality
s in an open-label, single-arm, multi-center study. The major
ıs to 5 mg daily and 5 mg every other day, as well as dose

s having received ≥ 2 units of RBCs within 8 weeks prior to
um creatinine ≤ 2.5 mg/dL, serum SGOT/AST or SGPT/ALT ≤
nts who developed neutropenia or fever in association with

Overall (N=148)
71.0 37.0, 95.0
(%)
(34.5)
(65.5)
(%)
(96.6)
(3.4)
2.5 0.1, 20.7
(%)
(100.0)
(25.2)
(%)
(37.2)
(43.9)
(4.1)
(1.4)
(13.5)
(%)
(52.0)
(10.8)
(20.3)
(2.0)

) response criteria for MDS. RBC transfusion independence
d.

sfusion independence was first declared (i.e., the last day of
period among the 99 responders was 44 weeks (range of 0

ts; the median time to the first dose reduction or interruption
.5 days; range, 2 to 265 days). A second dose reduction or
ond dose reduction or interruption was 51 days (mean, 59.7
days).

alidomide in patients with mantle cell lymphoma who have
min were given lenalidomide at a dose of 25 mg once daily
10 mg once daily for 21 days every 28 days. Treatment was

nts were required to have received prior treatment with an
ave documented refractory disease (defined as without any
progression within one year after treatment with bortezomib
t counts ≥ 60,000/mm³, serum SGOT/AST or SGPT/ALT ≤3x
ULN except in cases of Gilbert's syndrome or documented

ase-related characteristics and prior antilymphoma therapy

Total Patients (N=134)
43 (32) 73 (54) 17 (13) 1 (<1)
27 (20) 97 (72)
90 (67)
77 (57)
44 (33)
101 (75)
4 (2, 10)

• **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:
o yellowing of your skin or the white part of your eyes (jaundice)
o dark or brown (tea- colored) urine
o pain on the upper right side of your stomach area (abdomen)
o bleeding or bruising more easily than normal
o feeling very tired

• **Severe skin reactions including severe allergic reactions** can happen with lenalidomide capsules and may cause death. Call your healthcare provider right away if you develop any of these signs or symptoms of a severe allergic reaction or severe skin reaction during treatment with lenalidomide capsules.
o swelling of your face, eyes, lips, tongue, throat
o trouble swallowing
o trouble breathing
o skin rash, hives, or peeling of your skin
o blisters
o rash with fever and or swollen glands
• **Tumor lysis syndrome (TLS).** TLS is caused by the fast breakdown of cancer cells. TLS can cause kidney failure and the need for dialysis treatment, abnormal heart rhythm, seizure and sometimes death. Your healthcare provider may do blood tests to check you for TLS.
• **Worsening of your tumor (tumor flare reaction).** Tell your healthcare provider if you get any of these symptoms of tumor flare reaction while taking 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
• constipation
• itching
• rash
• tiredness
• swelling of the limbs and skin
• nausea
• fever
• cough

These are not all the possible side effects of lenalidomide capsules.
Call your doctor for medical advice about side effects.
How should I store lenalidomide capsules?
• Store lenalidomide capsules below 30°C.
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 5 mg, 10 mg, 15 mg and 25 mg capsule shell contains gelatin and titanium dioxide.
Each capsule is printed with black ink, which includes black iron oxide, potassium hydroxide, propylene glycol, and shellac.

Manufactured by
Natco Pharma Limited Kothur-509228
Rangareddy District Telangana, India

Packed by:
Pharmaline - Lebanon
Liscensed by:
Natco Pharma Limited, India

Revised: 11/2018

Rev. 11/2018 905267-A

Dexamethasone was dosed 40 mg once daily on Days 1, 8, 15, and 22
ily on days 1,8,15, and 22 of repeated 28-day cycles. Initial dose and
ctic anticoagulation with the most commonly used being aspirin.
eneral, study subjects had advanced-stage disease. Of the total study
had ISS stage III; 9% had severe renal impairment (creatinine clearance
> 50 to 80 mL/min). For ECOG Performance Status, 29% were Grade 0,

documentation of disease progression as determined by independent
o any cause, whichever occurred first during the study until the end of
and MPT arms. The efficacy results are summarized in the table below.
of subjects in the Rd Continuous arm compared with the MPT arm had
the MPT arm was 4.3 months. The myeloma response rate was higher
atients versus 9.3% in the MPT arm. The median time to first response

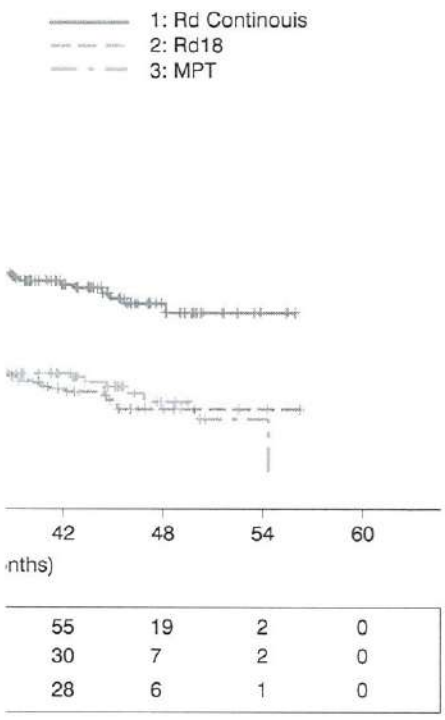
onths, with 697 death events, representing 78% of prespecified events
uous versus MPT (95% CI = 0.62, 0.90).

Rd18 (N = 541)	MPT (N = 547)
348 (64.3)	334 (61.1)
20.7 (19.4, 22.0)	21.2 (19.3, 23.2)
0.72 (0.61, 0.85); <0.0001	
0.70 (0.60, 0.82)	
1.03 (0.89, 1.20)	
228 (42.1)	261 (47.7)
56.7 (50.1, NE)	48.5 (44.2, 52.0)
0.75 (0.62, 0.90)	
0.91 (0.75, 1.09)	
0.83 (0.69, 0.99)	
77 (14.2)	51 (9.3)
154 (28.5)	103 (18.8)
166 (30.7)	187 (34.2)
397 (73.4)	341 (62.3)

Committee;
onse; R = lenalidomide; Rd Continuous = Rd given until documentation

s.
nt arms.

IRAC Assessment (ITT Population)
and MPT



55	19	2	0
30	7	2	0
28	6	1	0

k

.3%) MPT=334/547 (61.1%)

ion Committee; M = melphalan; P = prednisone; R = lenalidomide; Rd

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

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

Table 18: 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 1 2 3	 43 (32) 73 (54) 17 (13) 1 (<1)
Advanced MCL Stage, n (%) III IV	 27 (20) 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) 1 2 3 ≥ 4	 4 (2, 10) 0 (0) 29 (22) 34 (25) 71 (53)
Number of Subjects Who Received Prior Regimen Containing, n (%) Anthracycline/mitoxantrone Cyclophosphamide Rituximab Bortezomib	 133 (99) 133 (99) 134 (100) 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)

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

The efficacy endpoints in the MCL trial were overall response rate (ORR) and duration of response (DOR). Response was determined based on review of radiographic scans by an independent review committee according to a modified version of the International Workshop Lymphoma Response Criteria (Cheson, 1999). The DOR is defined as the time from the initial response (at least PR) to documented disease progression. The efficacy results for the MCL population were based on all evaluable patients who received at least one dose of study drug and are presented in Table 19. The median time to response was 2.2 months (range 1.8 to 13 months).

Table 19: 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

5 mg – Each #2 capsule with white opaque cap and body printed with NAT on cap and 5 mg on body in black ink contains 5 mg of lenalidomide.
5 mg bottles of 21

10 mg – Each #2 capsule with white opaque cap and body printed with NAT on cap and 10 mg on body in black ink contains 10 mg of lenalidomide.
10 mg bottles of 21
15 mg – Each #2 capsule with white opaque cap and body printed with NAT on cap and 15 mg on body in black ink contains 15 mg of lenalidomide.
15 mg bottles of 21

25 mg – Each #2 capsule with white opaque cap and body printed with NAT on cap and 25 mg on body in black ink contains 25 mg of lenalidomide.
25 mg bottles of 21

16.2 Storage

Store below 30°C.

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 Patient labeling (Medication Guide)

Embryo-Fetal Toxicity

Advise patients that lenalidomide is 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 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 *[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)]*.

Hematologic Toxicity

Inform patients that lenalidomide is associated with significant neutropenia and thrombocytopenia *[see Boxed Warning and Warnings and Precautions (5.2)]*.

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 Warning and Precautions (5.3)]*.