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

4 CONTRAINDICATIONS

4.1 Pregnancy

REVLIMID can cause fetal harm when administered to a pregnant female. Limb abnormalities were seen in the offspring of monkeys that were dosed with lenalidomide during organogenesis. This effect was seen at all doses tested. Due to the results of this developmental monkey study, and lenalidomide’s structural similarities to thalidomide, a known human teratogen, lenalidomide is contraindicated in females who are pregnant *[see Boxed Warning]*. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to a fetus *[see Warnings and Precautions (5.1, 5.2), Use in Special Populations (8.1, 8.3)]*.

4.2 Severe Hypersensitivity Reactions

REVLIMID is contraindicated in patients who have demonstrated severe hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide *[see Warnings and Precautions (5.8)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

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

REVLIMID is only available through the REVLIMID REMS program *[see Warnings and Precautions (5.2)]*.

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

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

Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing REVLIMID therapy and then weekly during the first month, then monthly thereafter in 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 REVLIMID and for up to 4 weeks after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm *[see Use in Specific Populations (8.3)]*.

Blood Donation
Patients must not donate blood during treatment with REVLIMID 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 REVLIMID.

5.2 REVLIMID REMS Program

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

Required components of the **REVLIMID REMS** program include the following:
- Prescribers must be certified with the **REVLIMID REMS** program by enrolling and complying with the REMS requirements.
- Patients must sign a Patient-Physician agreement form and comply with the REMS requirements. In particular, female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.3)]* and males must comply with contraception requirements *[see Use in Specific Populations (8.3)]*.
- Pharmacies must be certified with the **REVLIMID REMS** program, must only dispense to patients who are authorized to receive REVLIMID and comply with REMS requirements.

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

5.3 Hematologic Toxicity

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

Patients taking REVLIMID in combination with dexamethasone or as REVLIMID maintenance therapy 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)]*. In the MM maintenance therapy trials, Grade 3 or 4 neutropenia was reported in up to 59% of REVLIMID-treated patients and Grade 3 or 4 thrombocytopenia in up to 38% of REVLIMID-treated patients *[see Adverse Reactions (6.1)]*.

Patients taking REVLIMID for MDS should have their complete blood counts monitored weekly for the first 8 weeks and at least monthly thereafter. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the MDS study. In the 48% of patients who developed Grade 3 or 4 neutropenia, the median time to onset was 42 days (range, 14-411 days), and the median time to documented recovery was 17 days (range, 2-170 days). In the 54% of patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was 28 days (range, 8-290 days), and the median time to documented recovery was 22 days (range, 5-224 days) *[see Boxed Warning and Dosage and Administration (2.2)]*.

Patients taking REVLIMID for MCL should have their complete blood counts monitored weekly for the first cycle (28 days), every 2 weeks during cycles 2-4, and then monthly thereafter. Patients may require dose interruption and/or dose reduction. In the MCL trial, Grade 3 or 4 neutropenia was reported in 43% of the patients. Grade 3 or 4 thrombocytopenia was reported in 28% of the patients.

5.4 Venous and Arterial Thromboembolism

Venous thromboembolic events (VTE [DVT and PE]) and arterial thromboembolic events (ATE, myocardial infarction and stroke) are increased in patients treated with REVLIMID.

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 REVLIMID and dexamethasone therapy compared to patients treated in the placebo and dexamethasone group (3.1% and 0.9%) in clinical trials with varying use of anticoagulant therapies. In the newly diagnosed multiple myeloma (NDMM) study in which nearly all patients received antithrombotic prophylaxis, DVT was reported as a serious adverse reaction (3.6%, 2.0%, and 1.7%) in the Rd Continuous, Rd18, and MPT Arms, respectively. The frequency of serious adverse reactions of PE was similar between the Rd Continuous, Rd18, and MPT Arms (3.8%, 2.8%, and 3.7%, respectively) *[see Boxed Warning and Adverse Reactions (6.1)]*.

Myocardial infarction (1.7%) and stroke (CVA) (2.3%) are increased in patients with MM after at least one prior therapy who were treated with REVLIMID and dexamethasone therapy compared to patients treated with placebo and dexamethasone (0.6%, and 0.9%) in clinical trials. In the NDMM study, myocardial infarction (including acute) was reported as a serious adverse reaction (2.3%, 0.6%, and 1.1%) in the Rd Continuous, Rd18, and MPT Arms, respectively. The frequency of serious adverse reactions of CVA was similar between the Rd Continuous, Rd18, and MPT Arms (0.8%, 0.6 %, and 0.6%, respectively) *[see Adverse Reactions (6.1)]*.

Patients with known risk factors, including prior thrombosis, may be at greater risk and actions should be taken to try to minimize all modifiable factors (e.g. hyperlipidemia, hypertension, smoking).

In controlled clinical trials that did not use concomitant thromboprophylaxis, 21.5% overall thrombotic events (Standardized MedDRA Query Embolic and Thrombotic events) occurred in patients with refractory and relapsed MM who were treated with REVLIMID and dexamethasone compared to 8.3% thrombosis in patients treated with placebo and dexamethasone. The median time to first thrombosis event was 2.8 months. In the NDMM study in which nearly all patients received antithrombotic prophylaxis, the overall frequency of thrombotic events was 17.4% in patients in the combined Rd Continuous and Rd18 Arms, and was 11.6% in the MPT Arm. The median time to first thrombosis event was 4.3 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 REVLIMID *[see Drug Interactions (7.2)]*.

5.5 Increased Mortality in Patients with CLL

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

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

5.6 Second Primary Malignancies

In clinical trials in patients with MM receiving REVLIMID, 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 REVLIMID in combination with oral melphalan compared with 1.3% of patients receiving melphalan without REVLIMID. The frequency of AML and MDS cases in patients with NDMM treated with REVLIMID in combination with dexamethasone without melphalan was 0.4%.

In patients receiving REVLIMID maintenance therapy following high dose intravenous melphalan and auto-HSCT, hematologic SPM occurred in 7.5% of patients compared to 3.3% in patients receiving placebo. The incidence of hematologic plus solid tumor (excluding squamous cell carcinoma and basal cell carcinoma) SPM was 14.9%, compared to 8.8% in patients receiving placebo with a median follow-up of 91.5 months. Non-melanoma skin cancer SPM, including squamous cell carcinoma and basal cell carcinoma, occurred in 3.9% of patients receiving REVLIMID maintenance, compared to 2.6% in the placebo arm.

In patients with relapsed or refractory MM treated with REVLIMID/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 REVLIMID/dexamethasone, compared to 0.6% in the dexamethasone alone arm.

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

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

No PD-1 or PD-L1 blocking antibodies are approved for the treatment of MM. In two randomized clinical trials in patients with MM, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone resulted in increased mortality. In Study KN183 (NCT02576977), patients with relapsed or refractory MM were randomized to receive pomalidomide and dexamethasone with (n=125) or without (n=124) pembrolizumab. The hazard ratio for overall survival (OS) was 1.61 (95% CI: 0.91, 2.85), increasing the relative risk of death by more than 50% in the experimental arm containing pembrolizumab. Causes of death in the experimental arm, excluding disease progression, included: myocarditis, Stevens-Johnson syndrome, myocardial infarction, pericardial hemorrhage, cardiac failure, respiratory tract infection, neutropenic sepsis, sepsis, multiple organ dysfunction, and respiratory failure. In Study KN185 (NCT02579863), patients with NDMM were randomized to receive lenalidomide and dexamethasone with (n=151) or without (n=150) pembrolizumab. The hazard ratio for OS was 2.06 (95% CI: 0.93, 4.55), increasing the relative risk of death by more than 100% in the experimental arm containing pembrolizumab. Causes of death in the experimental arm, excluding disease progression, included: intestinal ischemia, cardio-respiratory arrest, suicide, pulmonary embolism, cardiac arrest, pneumonia, sudden death, myocarditis, large intestine perforation, and cardiac failure.

The addition of a PD-1 or PD-L1 blocking antibody to a thalidomide analogue is not recommended for the treatment of patients with MM outside of controlled clinical trials.

5.8 Hepatotoxicity

Hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dexamethasone. In clinical trials, 15% of patients experienced hepatotoxicity (with hepatocellular, cholestatic and mixed characteristics); 2% of patients with MM and 1% of patients with myelodysplasia had serious hepatotoxicity events. The mechanism of drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop REVLIMID upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

5.9 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 REVLIMID. REVLIMID interruption or discontinuation should be considered for Grade 2-3 skin rash. REVLIMID must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS, TEN or DRESS is suspected and should not be resumed following discontinuation for these reactions.

5.10 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.

5.11 Tumor Flare Reaction

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

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

5.12 Impaired Stem Cell Mobilization

A decrease in the number of CD34+ cells collected after treatment (> 4 cycles) with REVLIMID has been reported. In patients who are 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 REVLIMID-containing treatment or for whom inadequate numbers of CD 34+ cells have been collected with G-CSF alone, G-CSF with cyclophosphamide or the combination of G-CSF with a CXCR4 inhibitor may be considered.

5.13 Thyroid Disorders

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

5.14 Early Mortality in Patients with MCL

In another MCL study, there was an increase in early deaths (within 20 weeks), 12.9% in the REVLIMID 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).

6 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, 5.2)]*
- Hematologic Toxicity *[see Boxed Warning, Warnings and Precautions (5.3)]*
- Venous and Arterial Thromboembolism *[see Boxed Warning, Warnings and Precautions (5.4)]*
- Increased Mortality in Patients with CLL *[see Warnings and Precautions (5.5)]*
- Second Primary Malignancies *[see Warnings and Precautions (5.6)]*
- Increased Mortality in MM When Pembrolizumab Is Added to Dexamethasone and a Thalidomide Analogue *[see Warnings and Precautions (5.7)]*
- Hepatotoxicity *[see Warnings and Precautions (5.8)]*
- Severe Cutaneous Reactions Including Hypersensitivity Reactions *[see Warnings and Precautions (5.9)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.10)]*
- Tumor Flare Reactions *[see Warnings and Precautions (5.11)]*
- Impaired Stem Cell Mobilization *[see Warnings and Precautions (5.12)]*

- Thyroid Disorders *[see Warnings and Precautions (5.13)]*
- Early Mortality in Patients with MCL *[see Warnings and Precautions (5.14)]*

6.1 Clinical Trials Experience

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

Newly Diagnosed MM – REVLIMID Combination Therapy:

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

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

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

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

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

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

	All Adverse Reactions[a]			Grade 3/4 Adverse Reactions[b]		
Body System Adverse Reaction	**Rd Continuous (N = 532)**	**Rd18 (N = 540)**	**MPT (N = 541)**	**Rd Continuous (N = 532)**	**Rd18 (N = 540)**	**MPT (N = 541)**
General disorders and administration site conditions						
Fatigue[%]	173 (32.5)	177 (32.8)	154 (28.5)	39 (7.3)	46 (8.5)	31 (5.7)
Asthenia	150 (28.2)	123 (22.8)	124 (22.9)	41 (7.7)	33 (6.1)	32 (5.9)
Pyrexia[c]	114 (21.4)	102 (18.9)	76 (14.0)	13 (2.4)	7 (1.3)	7 (1.3)
Non-cardiac chest pain[f]	29 (5.5)	31 (5.7)	18 (3.3)	<1%	< 1%	< 1%
Gastrointestinal disorders						
Diarrhea	242 (45.5)	208 (38.5)	89 (16.5)	21 (3.9)	18 (3.3)	8 (1.5)
Abdominal pain[%,f]	109 (20.5)	78 (14.4)	60 (11.1)	7 (1.3)	9 (1.7)	< 1%
Dyspepsia[f]	57 (10.7)	28 (5.2)	36 (6.7)	<1%	< 1%	0 (0.0)
Musculoskeletal and connective tissue disorders						
Back pain[c]	170 (32.0)	145 (26.9)	116 (21.4)	37 (7.0)	34 (6.3)	28 (5.2)
Muscle spasms[f]	109 (20.5)	102 (18.9)	61 (11.3)	< 1%	< 1%	< 1%
Arthralgia[f]	101 (19.0)	71 (13.1)	66 (12.2)	9 (1.7)	8 (1.5)	8 (1.5)
Bone pain[f]	87 (16.4)	77 (14.3)	62 (11.5)	16 (3.0)	15 (2.8)	14 (2.6)
Pain in extremity[f]	79 (14.8)	66 (12.2)	61 (11.3)	8 (1.5)	8 (1.5)	7 (1.3)
Musculoskeletal pain[f]	67 (12.6)	59 (10.9)	36 (6.7)	< 1%	< 1%	< 1%
Musculoskeletal chest pain[f]	60 (11.3)	51 (9.4)	39 (7.2)	6 (1.1)	< 1%	< 1%
Muscular weakness[f]	43 (8.1)	35 (6.5)	29 (5.4)	< 1%	8 (1.5)	< 1%
Neck pain[f]	40 (7.5)	19 (3.5)	10 (1.8)	< 1%	< 1%	< 1%
Infections and infestations						
Bronchitis[c]	90 (16.9)	59 (10.9)	43 (7.9)	9 (1.7)	6 (1.1)	3 (0.6)
Nasopharyngitis[f]	80 (15.0)	54 (10.0)	33 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary tract infection[f]	76 (14.3)	63 (11.7)	41 (7.6)	8 (1.5)	8 (1.5)	< 1%
Upper respiratory tract infection[c,%,f]	69 (13.0)	53 (9.8)	31 (5.7)	< 1%	8 (1.5)	< 1%
Pneumonia[c,@]	93 (17.5)	87 (16.1)	56 (10.4)	60 (11.3)	57 (10.5)	41 (7.6)
Respiratory tract infection[%]	35 (6.6)	25 (4.6)	21 (3.9)	7 (1.3)	4 (0.7)	1 (0.2)

Body System Adverse Reaction	All Adverse Reactions[a]			Grade 3/4 Adverse Reactions[b]		
	Rd Continuous (N = 532)	Rd18 (N = 540)	MPT (N = 541)	Rd Continuous (N = 532)	Rd18 (N = 540)	MPT (N = 541)
Influenza[f]	33 (6.2)	23 (4.3)	15 (2.8)	< 1%	< 1%	0 (0.0)
Gastroenteritis[f]	32 (6.0)	17 (3.1)	13 (2.4)	0 (0.0)	< 1%	< 1%
Lower respiratory tract infection	29 (5.5)	14 (2.6)	16 (3.0)	10 (1.9)	3 (0.6)	3 (0.6)
Rhinitis[f]	29 (5.5)	24 (4.4)	14 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Cellulitis[c]	< 5%	< 5%	< 5%	8 (1.5)	3 (0.6)	2 (0.4)
Sepsis[c@]	33 (6.2)	26 (4.8)	18 (3.3)	26 (4.9)	20 (3.7)	13 (2.4)
Nervous system disorders						
Headache[f]	75 (14.1)	52 (9.6)	56 (10.4)	< 1%	< 1%	< 1%
Dysgeusia[f]	39 (7.3)	45 (8.3)	22 (4.1)	< 1%	0 (0.0)	< 1%
Blood and lymphatic system disorders[d]						
Anemia	233 (43.8)	193 (35.7)	229 (42.3)	97 (18.2)	85 (15.7)	102 (18.9)
Neutropenia	186 (35.0)	178 (33.0)	328 (60.6)	148 (27.8)	143 (26.5)	243 (44.9)
Thrombocytopenia	104 (19.5)	100 (18.5)	135 (25.0)	44 (8.3)	43 (8.0)	60 (11.1)
Febrile neutropenia	7 (1.3)	17 (3.1)	15 (2.8)	6 (1.1)	16 (3.0)	14 (2.6)
Pancytopenia	5 (0.9)	6 (1.1)	7 (1.3)	1 (0.2)	3 (0.6)	5 (0.9)
Respiratory, thoracic and mediastinal disorders						
Cough[f]	121 (22.7)	94 (17.4)	68 (12.6)	< 1%	< 1%	< 1%
Dyspnea[c,e]	117 (22.0)	89 (16.5)	113 (20.9)	30 (5.6)	22 (4.1)	18 (3.3)
Epistaxis[f]	32 (6.0)	31 (5.7)	17 (3.1)	< 1%	< 1%	0 (0.0)
Oropharyngeal pain[f]	30 (5.6)	22 (4.1)	14 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnea exertional[e]	27 (5.1)	29 (5.4)	< 5%	6 (1.1)	2 (0.4)	0 (0.0)
Metabolism and nutrition disorders						
Decreased appetite	123 (23.1)	115 (21.3)	72 (13.3)	14 (2.6)	7 (1.3)	5 (0.9)
Hypokalemia[%]	91 (17.1)	62 (11.5)	38 (7.0)	35 (6.6)	20 (3.7)	11 (2.0)
Hyperglycemia	62 (11.7)	52 (9.6)	19 (3.5)	28 (5.3)	23 (4.3)	9 (1.7)
Hypocalcemia	57 (10.7)	56 (10.4)	31 (5.7)	23 (4.3)	19 (3.5)	8 (1.5)
Dehydration[%]	25 (4.7)	29 (5.4)	17 (3.1)	8 (1.5)	13 (2.4)	9 (1.7)
Gout[e]	< 5%	< 5%	< 5%	8 (1.5)	0 (0.0)	0 (0.0)
Diabetes mellitus[%,e]	< 5%	< 5%	< 5%	8 (1.5)	4 (0.7)	2 (0.4)
Hypophosphatemia[e]	< 5%	< 5%	< 5%	7 (1.3)	3 (0.6)	1 (0.2)
Hyponatremia[%,e]	< 5%	< 5%	< 5%	7 (1.3)	13 (2.4)	6 (1.1)
Skin and subcutaneous tissue disorders						
Rash	139 (26.1)	151 (28.0)	105 (19.4)	39 (7.3)	38 (7.0)	33 (6.1)
Pruritus[f]	47 (8.8)	49 (9.1)	24 (4.4)	< 1%	< 1%	< 1%
Psychiatric disorders						
Insomnia	147 (27.6)	127 (23.5)	53 (9.8)	4 (0.8)	6 (1.1)	0 (0.0)
Depression	58 (10.9)	46 (8.5)	30 (5.5)	10 (1.9)	4 (0.7)	1 (0.2)
Vascular disorders						
Deep vein thrombosis[c%]	55 (10.3)	39 (7.2)	22 (4.1)	30 (5.6)	20 (3.7)	15 (2.8)
Hypotension[c%]	51 (9.6)	35 (6.5)	36 (6.7)	11 (2.1)	8 (1.5)	6 (1.1)
Injury, Poisoning, and Procedural Complications						
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)

Body System Adverse Reaction	All Adverse Reactions[a]			Grade 3/4 Adverse Reactions[b]		
	Rd Continuous (N = 532)	Rd18 (N = 540)	MPT (N = 541)	Rd Continuous (N = 532)	Rd18 (N = 540)	MPT (N = 541)
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@,f]	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 e,f]	< 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.

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

[e] Footnote "a" not applicable

[f] Footnote "b" not applicable.

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

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

*Adverse reactions 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

Newly Diagnosed MM - REVLIMID Maintenance Therapy Following Auto-HSCT:

Data were evaluated from 1018 patients in two randomized trials who received at least one dose of REVLIMID 10 mg daily as maintenance therapy after auto-HSCT until progressive disease or unacceptable toxicity, The mean treatment duration for REVLIMID treatment was 30.3 months for Maintenance Study 1 and 24.0 months for Maintenance Study 2 (overall range across both studies from 0.1 to 108 months). As of the cut-off date of 1 Mar 2015, 48 patients (21%) in the Maintenance Study 1 REVLIMID arm were still on treatment and none of the patients in the Maintenance Study 2 REVLIMID arm were still on treatment at the same cut-off date

The adverse reactions listed from Maintenance Study 1 included events reported post-transplant (completion of high-dose melphalan /auto-HSCT), and the maintenance treatment period. In Maintenance Study 2, the adverse reactions were from the maintenance treatment period only. In general, the most frequently reported adverse reactions (more than 20% in the REVLIMID arm) across both studies were neutropenia, thrombocytopenia, leukopenia, anemia, upper respiratory tract infection, bronchitis, nasopharyngitis, cough, gastroenteritis, diarrhea, rash, fatigue, asthenia, muscle spasm and pyrexia. The most frequently reported Grade 3 or 4 reactions (more than 20% in the REVLIMID arm) included neutropenia, thrombocytopenia, and leukopenia. The serious adverse reactions lung infection and neutropenia (more than 4.5%) occurred in the REVLIMID arm.

For REVLIMID, the most common adverse reactions leading to dose interruption were hematologic events (29.7%, data available in Maintenance Study 2 only). The most common adverse reaction leading to dose reduction of REVLIMID were hematologic events (17.7%, data available in Maintenance Study 2 only). The most common adverse reactions leading to discontinuation of REVLIMID were thrombocytopenia (2.7%) in Maintenance Study 1 and neutropenia (2.4%) in Maintenance Study 2.

The frequencies of onset of adverse reactions were generally highest in the first 6 months of treatment and then the frequencies decreased over time or remained stable throughout treatment.

Table 5 summarizes the adverse reactions reported for the REVLIMID and placebo maintenance treatment arms.

Table 5: All Adverse Reactions in ≥5.0% and Grade 3/4 Adverse Reactions in ≥ 1.0% of Patients in the REVLIMID Vs Placebo Arms*

Body System Adverse Reaction	Maintenance Study 1				Maintenance Study 2			
	All Adverse Reactions [a]		Grade 3/4 Adverse Reactions [b]		All Adverse Reactions [a]		Grade 3/4 Adverse Reactions [b]	
	REVLIMID (N=224) n (%)	Placebo (N=221) n (%)	REVLIMID (N=224) n (%)	Placebo (N=221) n (%)	REVLIMID (N=293) n (%)	Placebo (N=280) n (%)	REVLIMID (N=293) n (%)	Placebo (N=280) n (%)
Blood and lymphatic system disorders								
Neutropenia [c %]	177 (79.0)	94 (42.5)	133 (59.4)	73 (33.0)	178 (60.8)	33 (11.8)	158 (53.9)	21 (7.5)

Body System Adverse Reaction	Maintenance Study 1				Maintenance Study 2			
	All Adverse Reactions [a]		Grade 3/4 Adverse Reactions [b]		All Adverse Reactions [a]		Grade 3/4 Adverse Reactions [b]	
	REVLIMID (N=224) n (%)	Placebo (N=221) n (%)	REVLIMID (N=224) n (%)	Placebo (N=221) n (%)	REVLIMID (N=293) n (%)	Placebo (N=280) n (%)	REVLIMID (N=293) n (%)	Placebo (N=280) n (%)
Thrombocytopenia [c %]	162 (72.3)	101 (45.7)	84 (37.5)	67 (30.3)	69 (23.5)	29 (10.4)	38 (13.0)	8 (2.9)
Leukopenia [c]	51 (22.8)	25 (11.3)	45 (20.1)	22 (10.0)	93 (31.7)	21 (7.5)	71 (24.2)	5 (1.8)
Anemia	47 (21.0)	27 (12.2)	23 (10.3)	18 (8.1)	26 (8.9)	15 (5.4)	11 (3.8)	3 (1.1)
Lymphopenia	40 (17.9)	29 (13.1)	37 (16.5)	26 (11.8)	13 (4.4)	3 (1.1)	11 (3.8)	2 (0.7)
Pancytopenia [c d %]	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	12 (4.1)	1 (0.4)	7 (2.4)	1 (0.4)
Febrile neutropenia [c]	39 (17.4)	34 (15.4)	39 (17.4)	34 (15.4)	7 (2.4)	1 (0.4)	5 (1.7)	1 (0.4)
Infections and infestations[#]								
Upper respiratory tract infection [e]	60 (26.8)	35 (15.8)	7 (3.1)	9 (4.1)	32 (10.9)	18 (6.4)	1 (0.3)	0 (0.0)
Neutropenic infection	40 (17.9)	19 (8.6)	27 (12.1)	14 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonias* [c %]	31 (13.8)	15 (6.8)	23 (10.3)	7 (3.2)	50 (17.1)	13 (4.6)	27 (9.2)	5 (1.8)
Bronchitis [c]	10 (4.5)	9 (4.1)	1 (0.4)	5 (2.3)	139 (47.4)	104 (37.1)	4 (1.4)	1 (0.4)
Nasopharyngitis [e]	5 (2.2)	2 (0.9)	0 (0.0)	0 (0.0)	102 (34.8)	84 (30.0)	1 (0.3)	0 (0.0)
Gastroenteritis [c]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	66 (22.5)	55 (19.6)	6 (2.0)	0 (0.0)
Rhinitis [e]	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	44 (15.0)	19 (6.8)	0 (0.0)	0 (0.0)
Sinusitis [e]	8 (3.6)	3 (1.4)	0 (0.0)	0 (0.0)	41 (14.0)	26 (9.3)	0 (0.0)	1 (0.4)
Influenza [c]	8 (3.6)	5 (2.3)	2 (0.9)	1 (0.5)	39 (13.3)	19 (6.8)	3 (1.0)	0 (0.0)
Lung infection [c]	21 (9.4)	2 (0.9)	19 (8.5)	2 (0.9)	9 (3.1)	4 (1.4)	1 (0.3)	0 (0.0)
Lower respiratory tract infection [e]	13 (5.8)	5 (2.3)	6 (2.7)	4 (1.8)	4 (1.4)	4 (1.4)	0 (0.0)	2 (0.7)
Infection [c]	12 (5.4)	6 (2.7)	9 (4.0)	5 (2.3)	17 (5.8)	5 (1.8)	0 (0.0)	0 (0.0)
Urinary tract infection [c d e]	9 (4.0)	5 (2.3)	4 (1.8)	4 (1.8)	22 (7.5)	17 (6.1)	1 (0.3)	0 (0.0)
Lower respiratory tract infection bacterial [d]	6 (2.7)	1 (0.5)	4 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bacteremia [d]	5 (2.2)	0 (0.0)	4 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Herpes zoster [c d]	11 (4.9)	10 (4.5)	3 (1.3)	2 (0.9)	29 (9.9)	25 (8.9)	6 (2.0)	2 (0.7)
Sepsis* [c d @]	2 (0.9)	1 (0.5)	0 (0.0)	0 (0.0)	6 (2.0)	1 (0.4)	4 (1.4)	1 (0.4)
Gastrointestinal disorders								
Diarrhea	122 (54.5)	83 (37.6)	22 (9.8)	17 (7.7)	114 (38.9)	34 (12.1)	7 (2.4)	0 (0.0)
Nausea [e]	33 (14.7)	22 (10.0)	16 (7.1)	10 (4.5)	31 (10.6)	28 (10.0)	0 (0.0)	0 (0.0)
Vomiting	17 (7.6)	12 (5.4)	8 (3.6)	5 (2.3)	16 (5.5)	15 (5.4)	1 (0.3)	0 (0.0)
Constipation [e]	12 (5.4)	8 (3.6)	0 (0.0)	0 (0.0)	37 (12.6)	25 (8.9)	2 (0.7)	0 (0.0)
Abdominal pain [e]	8 (3.6)	7 (3.2)	1 (0.4)	4 (1.8)	31 (10.6)	15 (5.4)	1 (0.3)	1 (0.4)
Abdominal pain upper [e]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	20 (6.8)	12 (4.3)	1 (0.3)	0 (0.0)
General disorders and administration site conditions								
Asthenia	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	87 (29.7)	53 (18.9)	10 (3.4)	2 (0.7)
Fatigue	51 (22.8)	30 (13.6)	21 (9.4)	9 (4.1)	31 (10.6)	15 (5.4)	3 (1.0)	0 (0.0)
Pyrexia [e]	17 (7.6)	10 (4.5)	2 (0.9)	2 (0.9)	60 (20.5)	26 (9.3)	1 (0.3)	0 (0.0)
Skin and subcutaneous tissue disorders								
Dry skin [e]	9 (4.0)	4 (1.8)	0 (0.0)	0 (0.0)	31 (10.6)	21 (7.5)	0 (0.0)	0 (0.0)
Rash	71 (31.7)	48 (21.7)	11 (4.9)	5 (2.3)	22 (7.5)	17 (6.1)	3 (1.0)	0 (0.0)

Body System Adverse Reaction	Maintenance Study 1				Maintenance Study 2			
	All Adverse Reactions [a]		Grade 3/4 Adverse Reactions [b]		All Adverse Reactions [a]		Grade 3/4 Adverse Reactions [b]	
	REVLIMID (N=224) n (%)	Placebo (N=221) n (%)	REVLIMID (N=224) n (%)	Placebo (N=221) n (%)	REVLIMID (N=293) n (%)	Placebo (N=280) n (%)	REVLIMID (N=293) n (%)	Placebo (N=280) n (%)
Pruritus	9 (4.0)	4 (1.8)	3 (1.3)	0 (0.0)	21 (7.2)	25 (8.9)	2 (0.7)	0 (0.0)
Nervous system disorders								
Paresthesia [e]	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	39 (13.3)	30 (10.7)	1 (0.3)	0 (0.0)
Peripheral neuropathy* [c]	34 (15.2)	30 (13.6)	8 (3.6)	8 (3.6)	29 (9.9)	15 (5.4)	4 (1.4)	2 (0.7)
Headache [d]	11 (4.9)	8 (3.6)	5 (2.2)	1 (0.5)	25 (8.5)	21 (7.5)	0 (0.0)	0 (0.0)
Investigations								
Alanine aminotransferase increased	16 (7.1)	3 (1.4)	8 (3.6)	0 (0.0)	5 (1.7)	5 (1.8)	0 (0.0)	1 (0.4)
Aspartate aminotransferase increased [d]	13 (5.8)	5 (2.3)	6 (2.7)	0 (0.0)	2 (0.7)	5 (1.8)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders								
Hypokalemia	24 (10.7)	13 (5.9)	16 (7.1)	12 (5.4)	12 (4.1)	1 (0.4)	2 (0.7)	0 (0.0)
Dehydration	9 (4.0)	5 (2.3)	7 (3.1)	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypophosphatemia [d]	16 (7.1)	15 (6.8)	13 (5.8)	14 (6.3)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders								
Muscle spasms [e]	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	98 (33.4)	43 (15.4)	1 (0.3)	0 (0.0)
Myalgia [e]	7 (3.1)	8 (3.6)	3 (1.3)	5 (2.3)	19 (6.5)	12 (4.3)	2 (0.7)	1 (0.4)
Musculoskeletal pain [e]	1 (0.4)	1 (0.5)	0 (0.0)	0 (0.0)	19 (6.5)	11 (3.9)	0 (0.0)	0 (0.0)
Hepatobiliary disorders								
Hyperbilirubinemia [e]	34 (15.2)	19 (8.6)	4 (1.8)	2 (0.9)	4 (1.4)	1 (0.4)	2 (0.7)	0 (0.0)
Respiratory, thoracic and mediastinal disorders								
Cough [e]	23 (10.3)	12 (5.4)	3 (1.3)	1 (0.5)	80 (27.3)	56 (20.0)	0 (0.0)	0 (0.0)
Dyspnea [c e]	15 (6.7)	9 (4.1)	8 (3.6)	4 (1.8)	17 (5.8)	9 (3.2)	2 (0.7)	0 (0.0)
Rhinorrhea [e]	0 (0.0)	3 (1.4)	0 (0.0)	0 (0.0)	15 (5.1)	6 (2.1)	0 (0.0)	0 (0.0)
Pulmonary embolism [c d e]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)	2 (0.7)	0 (0.0)
Vascular disorders								
Deep vein thrombosis* [c d %]	8 (3.6)	2 (0.9)	5 (2.2)	2 (0.9)	7 (2.4)	1 (0.4)	4 (1.4)	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
Myelodysplastic syndrome [c d e]	5 (2.2)	0 (0.0)	2 (0.9)	0 (0.0)	3 (1.0)	0 (0.0)	1 (0.3)	0 (0.0)

Note: AEs are coded to body system /adverse reaction using MedDRA v15.1. A subject with multiple occurrences of an AE is counted only once in each AE category.

[a] All treatment-emergent AEs in at least 5% of patients in the Lenalidomide Maintenance group and at least 2% higher frequency (%) than the Placebo Maintenance group.

[b] All grade 3 or 4 treatment-emergent AEs in at least 1% of patients in the Lenalidomide Maintenance group and at least 1% higher frequency (%) than the Placebo Maintenance group.

[c] All serious treatment-emergent AEs in at least 1% of patients in the Lenalidomide Maintenance group and at least 1% higher frequency (%) than the Placebo Maintenance group.

[d] Footnote "a" not applicable for either study

[e] Footnote "b" not applicable for either study

@ -ADRs where at least one resulted in a fatal outcome

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

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

*Adverse Reactions for combined ADR terms (based on relevant TEAE PTs included in Maintenance Studies 1 and 2 [per MedDRA v 15.1]):

Pneumonias Bronchopneumonia,. Lobar pneumonia, Pneumocystis jiroveci pneumonia, Pneumonia, Pneumonia klebsiella, Pneumonia legionella, Pneumonia mycoplasmal, Pneumonia pneumococcal, Pneumonia streptococcal, Pneumonia viral, Lung disorder, Pneumonitis

Sepsis: Bacterial sepsis, Pneumococcal sepsis, Sepsis, Septic shock, Staphylococcal sepsis

Peripheral neuropathy: Neuropathy peripheral, Peripheral motor neuropathy, Peripheral sensory neuropathy, Polyneuropathy

Deep vein thrombosis: Deep vein thrombosis, Thrombosis, Venous thrombosis

After At Least One Prior Therapy for MM:

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

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

Tables 6, 7, and 8 summarize the adverse reactions reported for REVLIMID/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 REVLIMID/dexamethasone and Placebo/dexamethasone Groups

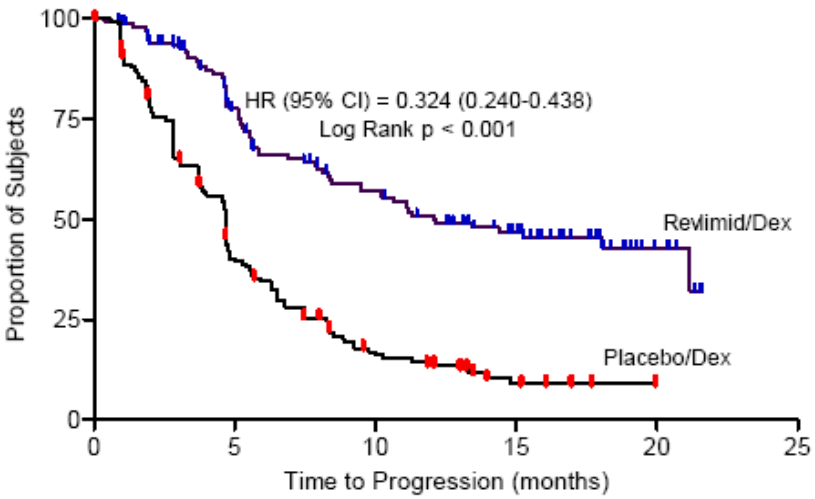
Body System Adverse Reaction	**REVLIMID/Dex* (N=353) n (%)**	**Placebo/Dex * (N=350) n (%)**
Blood and lymphatic system disorders		
Neutropenia[%]	149 (42.2)	22 (6.3)
Anemia[@]	111 (31.4)	83 (23.7)
Thrombocytopenia[@]	76 (21.5)	37 (10.6)
Leukopenia	28 (7.9)	4 (1.1)
Lymphopenia	19 (5.4)	5 (1.4)
General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

Body System Adverse Reaction	REVLIMID/Dex* (N=353) n (%)	Placebo/Dex * (N=350) n (%)
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 REVLIMID/dexamethasone and Placebo/dexamethasone groups

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

Kaplan-Meier Estimate of Time to Progression — Study 2



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

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

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

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

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

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

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

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

RBC transfusion independence rates were unaffected by age or gender.

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

14.3 Mantle Cell Lymphoma

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

16.2 Storage

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

16.3 Handling and Disposal

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

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

Dispense no more than a 28-day supply.

17 PATIENT COUNSELING INFORMATION

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

Embryo-Fetal Toxicity

Advise patients that REVLIMID is contraindicated in pregnancy *[see Boxed Warning and Contraindications (4.1)]*. REVLIMID 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 REVLIMID and for at least 4 weeks after completing therapy.
- Initiate REVLIMID treatment in females of reproductive potential only following a negative pregnancy test.
- Advise females of reproductive potential of the importance of monthly pregnancy tests and the need to use 2 different forms of contraception including at least 1 highly effective form, simultaneously during REVLIMID therapy, during dose interruption and for 4 weeks after she has completely finished taking REVLIMID. Highly effective forms of contraception other than tubal ligation include IUD and hormonal (birth control pills, injections, patch or implants) and a partner's vasectomy. Additional effective contraceptive methods include latex or synthetic condom, diaphragm and cervical cap.
- Instruct patient to immediately stop taking REVLIMID and contact her healthcare provider if she becomes pregnant while taking this drug, if she misses her menstrual period, or experiences unusual menstrual bleeding, if she stops taking birth control, or if she thinks FOR ANY REASON that she may be pregnant.
- Advise patient that if her healthcare provider is not available, she should call Celgene Customer Care Center at 1-888-423-5436 *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.3)]*.
- Advise males to always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 4 weeks after discontinuing REVLIMID, even if they have undergone a successful vasectomy.
- Advise male patients taking REVLIMID that they must not donate sperm *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.3)]*.
- All patients must be instructed to not donate blood while taking REVLIMID, during dose interruptions and for 4 weeks following discontinuation of REVLIMID *[see Warnings and Precautions (5.1)]*.

REVLIMID REMS program

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

- Patients must sign a Patient-Physician agreement form and comply with the requirements to receive REVLIMID. In particular, females of reproductive potential must comply with the pregnancy testing, contraception requirements and participate in monthly telephone surveys. Males must comply with the contraception requirements *[see Use in Specific Populations (8.3)]*.
- REVLIMID is available only from pharmacies that are certified in REVLIMID REMS program. Provide patients with the telephone number and website for information on how to obtain the product.

Pregnancy Exposure Registry

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

Hematologic Toxicity

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

Venous and Arterial Thromboembolism

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

Increased Mortality in Patients with CLL

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

Second Primary Malignancies

Inform patients of the potential risk of developing second primary malignancies during treatment with REVLIMID *[see Warnings and Precautions (5.6)]*.

Increased Mortality in MM Patients When Pembrolizumab Was Added to Dexamethasone and a Thalidomide Analogue Regimen

Inform patients of potential for increased risk of death in people with MM when a PD-1 blocking antibody was added to a dexamethasone and thalidomide analogue treatment regimen *[see Warnings and Precautions (5.7)]*.

Hepatotoxicity

Inform patients of the risk of hepatotoxicity, including hepatic failure and death, and to report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions (5.8)]*.

Severe Cutaneous Reactions 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 (5.9)]*.

Tumor Lysis Syndrome

Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions (5.10)]*.

Tumor Flare Reaction

Inform patients of the potential risk of tumor flare reaction and to report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions (5.11)]*.

Early Mortality in Patients with MCL

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

Dosing Instructions

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

- REVLIMID should be taken once daily at about the same time each day,
- REVLIMID may be taken either with or without food.
- The capsules should not be opened, broken, or chewed. REVLIMID should be swallowed whole with water.
- Instruct patients that if they miss a dose of REVLIMID, they may still take it up to 12 hours after the time they would normally take it. If more than 12 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take REVLIMID at the usual time. Warn patients to not take 2 doses to make up for the one that they missed.

Manufactured for: Celgene Corporation
Summit, NJ 07901

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