

































<b>Body System</b> Adverse Reaction	<b>REVLIMID/Dex*</b> (N=353) n (%)	<b>Placebo/Dex *</b> (N=350) n (%)
Appetite Decreased	24 ( 6.8)	14 ( 4.0)
Dehydration	23 ( 6.5)	15 ( 4.3)
Hypomagnesemia	24 ( 6.8)	10 ( 2.9)
<b>Investigations</b>		
Weight Decreased	69 (19.5)	52 (14.9)
<b>Eye disorders</b>		
Blurred vision	61 (17.3)	40 (11.4)
<b>Vascular disorders</b>		
Deep vein thrombosis <sup>%</sup>	33 ( 9.3)	15 ( 4.3)
Hypertension	28 ( 7.9)	20 ( 5.7)
Hypotension	25 ( 7.1)	15 ( 4.3)

**Table 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**

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



<b>Body System</b> Adverse Reaction	<b>REVLIMID/Dex<sup>#</sup></b> (N=353) n (%)	<b>Placebo/Dex<sup>#</sup></b> (N=350) n (%)
Cataract	6 ( 1.7)	1 ( 0.3)
Cataract Unilateral	5 ( 1.4)	0 ( 0.0)
<b>Psychiatric Disorder</b>		
Depression	10 ( 2.8)	6 ( 1.7)

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

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

For Tables 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 REVLIMID/dexamethasone was 44 weeks while median duration of exposure among patients treated with placebo/dexamethasone was 23 weeks. This should be taken into consideration when comparing frequency of adverse reactions between two treatment groups REVLIMID/dexamethasone vs. placebo/dexamethasone.

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

VTE and ATE are increased in patients treated with REVLIMID.

Deep vein thrombosis (DVT) was reported as a serious (7.4%) or severe (8.2%) adverse drug reaction at a higher rate in the REVLIMID/dexamethasone group compared to 3.1 % and 3.4% in the placebo/dexamethasone group, respectively in the 2 studies in patients with at least 1 prior therapy with discontinuations due to DVT adverse reactions reported at comparable rates between groups. In the NDMM study, DVT was reported as an adverse reaction (all grades: 10.3%, 7.2%, 4.1%), as a serious adverse reaction (3.6%, 2.0%, 1.7%), and as a Grade 3/4 adverse reaction (5.6%, 3.7%, 2.8%) in the Rd Continuous, Rd18, and MPT Arms, respectively. Discontinuations and dose reductions due to DVT adverse reactions were reported at comparable rates between the Rd Continuous and Rd18 Arms (both <1%). Interruption of REVLIMID treatment due to DVT adverse reactions was reported at comparable rates between the Rd Continuous (2.3%) and Rd18 (1.5%) arms. Pulmonary embolism (PE) was reported as a serious adverse drug reaction (3.7%) or Grade 3/4 (4.0%) at a higher rate in the REVLIMID/dexamethasone group compared to 0.9% (serious or grade 3/4) in the placebo/dexamethasone group in the 2 studies in patients with, at least 1 prior therapy, with discontinuations due to PE adverse reactions reported at comparable rates between groups. In the NDMM study, the frequency of adverse reactions of PE was similar between the Rd Continuous, Rd18, and MPT Arms for adverse reactions (all grades: 3.9%, 3.3%, and 4.3%, respectively), serious adverse reactions (3.8%, 2.8%, and 3.7%, respectively), and grade 3/4 adverse reactions (3.8%, 3.0%, and 3.7%, respectively).

Myocardial infarction was reported as a serious (1.7%) or severe (1.7%) adverse drug reaction at a higher rate in the REVLIMID/dexamethasone group compared to 0.6 % and 0.6% respectively in the placebo/dexamethasone group. Discontinuation due to MI (including acute) adverse reactions was 0.8% in REVLIMID/dexamethasone group and none in the placebo/dexamethasone group. In the NDMM study, myocardial infarction (including acute) was reported as an adverse reaction (all grades: 2.4%, 0.6%, and 1.1%), as a serious adverse reaction, (2.3%, 0.6%, and 1.1%), or as a severe adverse reaction (1.9%, 0.6%, and 0.9%) in the Rd Continuous, Rd18, and MPT Arms, respectively.

Stroke (CVA) was reported as a serious (2.3%) or severe (2.0%) adverse drug reaction in the REVLIMID/dexamethasone group compared to 0.9% and 0.9% respectively in the placebo/dexamethasone group. Discontinuation due to stroke (CVA) was 1.4% in REVLIMID/ dexamethasone group and 0.3% in the placebo/dexamethasone group. In the NDMM study, CVA was reported as an adverse reaction (all grades: 0.8%, 0.6%, and 0.6%), as a serious adverse reaction (0.8%, 0.6 %, and 0.6%), or as a severe adverse reaction (0.6%, 0.6%, 0.2%) in the Rd Continuous, Rd18, and MPT arms respectively.

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

In these 2 studies, the following adverse drug reactions (ADRs) not described above that occurred at  $\geq 1\%$  rate and of at least twice of the placebo percentage rate were reported:

**Blood and lymphatic system disorders:** pancytopenia, autoimmune hemolytic anemia

**Cardiac disorders:** bradycardia, myocardial infarction, angina pectoris

**Endocrine disorders:** hirsutism

**Eye disorders:** blindness, ocular hypertension

**Gastrointestinal disorders:** gastrointestinal hemorrhage, glossodynia

**General disorders and administration site conditions:** malaise

**Investigations:** liver function tests abnormal, alanine aminotransferase increased

**Nervous system disorders:** cerebral ischemia

**Psychiatric disorders:** mood swings, hallucination, loss of libido

**Reproductive system and breast disorders:** erectile dysfunction

**Respiratory, thoracic and mediastinal disorders:** cough, hoarseness

**Skin and subcutaneous tissue disorders:** exanthem, skin hyperpigmentation

**Myelodysplastic Syndromes:**

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

Thrombocytopenia (61.5%; 91/148) and neutropenia (58.8%; 87/148) were the most frequently reported adverse events. The next most common adverse events observed were diarrhea (48.6%; 72/148), pruritus (41.9%; 62/148), rash (35.8%; 53/148) and fatigue (31.1%; 46/148). Table 9 summarizes the adverse events that were reported in  $\geq 5\%$  of the REVLIMID 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 REVLIMID. In the single-arm studies conducted, it is often not possible to distinguish adverse events that are drug-related and those that reflect the patient's underlying disease.

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

<b>Body System</b>	<b>10 mg Overall</b>	
<b>Adverse Event</b> <sup>[a]</sup>	<b>(N=148)</b>	
Patients with at least one adverse event	148	(100.0)
<b>Blood and Lymphatic System Disorders</b>		
Thrombocytopenia	91	(61.5)
Neutropenia	87	(58.8)
Anemia	17	(11.5)
Leukopenia	12	(8.1)
Febrile Neutropenia	8	(5.4)
<b>Skin and Subcutaneous Tissue Disorders</b>		
Pruritus	62	(41.9)
Rash	53	(35.8)
Dry Skin	21	(14.2)
Contusion	12	(8.1)
Night Sweats	12	(8.1)
Sweating Increased	10	(6.8)
Ecchymosis	8	(5.4)
Erythema	8	(5.4)
<b>Gastrointestinal Disorders</b>		
Diarrhea	72	(48.6)
Constipation	35	(23.6)
Nausea	35	(23.6)
Abdominal Pain	18	(12.2)
Vomiting	15	(10.1)
Abdominal Pain Upper	12	(8.1)
Dry Mouth	10	(6.8)
Loose Stools	9	(6.1)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Nasopharyngitis	34	(23.0)
Cough	29	(19.6)
Dyspnea	25	(16.9)
Pharyngitis	23	(15.5)
Epistaxis	22	(14.9)
Dyspnea Exertional	10	(6.8)
Rhinitis	10	(6.8)
Bronchitis	9	(6.1)

<b>General Disorders and Administration Site Conditions</b>		
Fatigue	46	(31.1)
Pyrexia	31	(20.9)
Edema Peripheral	30	(20.3)
Asthenia	22	(14.9)
Edema	15	(10.1)
Pain	10	(6.8)
Rigors	9	(6.1)
Chest Pain	8	(5.4)
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Arthralgia	32	(21.6)
Back Pain	31	(20.9)
Muscle Cramp	27	(18.2)
Pain in Limb	16	(10.8)
Myalgia	13	(8.8)
Peripheral Swelling	12	(8.1)
<b>Nervous System Disorders</b>		
Dizziness	29	(19.6)
Headache	29	(19.6)
Hypoesthesia	10	(6.8)
Dysgeusia	9	(6.1)
Peripheral Neuropathy	8	(5.4)
<b>Infections and Infestations</b>		
Upper Respiratory Tract Infection	22	(14.9)
Pneumonia	17	(11.5)
Urinary Tract Infection	16	(10.8)
Sinusitis	12	(8.1)
Cellulitis	8	(5.4)
<b>Metabolism and Nutrition Disorders</b>		
Hypokalemia	16	(10.8)
Anorexia	15	(10.1)
Hypomagnesemia	9	(6.1)
<b>Investigations</b>		
Alanine Aminotransferase Increased	12	(8.1)
<b>Psychiatric Disorders</b>		
Insomnia	15	(10.1)
Depression	8	(5.4)
<b>Renal and Urinary Disorders</b>		
Dysuria	10	(6.8)
<b>Vascular Disorders</b>		
Hypertension	9	(6.1)
<b>Endocrine Disorders</b>		
Acquired Hypothyroidism	10	(6.8)
<b>Cardiac Disorders</b>		
Palpitations	8	(5.4)

<sup>[a]</sup> 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 <sup>[2]</sup>	10 mg (N=148)
Patients with at least one Grade 3/4 AE	131 (88.5)
Neutropenia	79 (53.4)
Thrombocytopenia	74 (50.0)
Pneumonia	11 (7.4)
Rash	10 (6.8)
Anemia	9 (6.1)
Leukopenia	8 (5.4)
Fatigue	7 (4.7)
Dyspnea	7 (4.7)
Back Pain	7 (4.7)
Febrile Neutropenia	6 (4.1)
Nausea	6 (4.1)
Diarrhea	5 (3.4)
Pyrexia	5 (3.4)
Sepsis	4 (2.7)
Dizziness	4 (2.7)
Granulocytopenia	3 (2.0)
Chest Pain	3 (2.0)

Pulmonary Embolism	3	(2.0)
Respiratory Distress	3	(2.0)
Pruritus	3	(2.0)
Pancytopenia	3	(2.0)
Muscle Cramp	3	(2.0)
Respiratory Tract Infection	2	(1.4)
Upper Respiratory Tract Infection	2	(1.4)
Asthenia	2	(1.4)
Multi-organ Failure	2	(1.4)
Epistaxis	2	(1.4)
Hypoxia	2	(1.4)
Pleural Effusion	2	(1.4)
Pneumonitis	2	(1.4)
Pulmonary Hypertension	2	(1.4)
Vomiting	2	(1.4)
Sweating Increased	2	(1.4)
Arthralgia	2	(1.4)
Pain in Limb	2	(1.4)
Headache	2	(1.4)
Syncope	2	(1.4)

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

<sup>[2]</sup> 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 REVLIMID 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

**Mantle Cell Lymphoma:**

In the MCL trial, a total of 134 patients received at least 1 dose of REVLIMID. Their median age was 67 (range 43-83) years, 128/134 (96%) were Caucasian, 108/134 (81%) were males and 82/134 (61%) had duration of MCL for at least 3 years.

Table 11 summarizes the most frequently observed adverse reactions regardless of relationship to treatment with REVLIMID. Across the 134 patients treated in this study, median duration of treatment was 95 days (1-1002 days). Seventy-eight patients (58%) received 3 or more cycles of therapy, 53 patients (40%) received 6 or more cycles, and 26 patients (19%) received 12 or more cycles. Seventy-six patients (57%) underwent at least one dose interruption due to adverse events, and 51 patients (38%) underwent at least one dose reduction due to adverse events. Twenty-six patients (19%) discontinued treatment due to adverse events.

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

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

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

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

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

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

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

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

<sup>#</sup> - All adverse reactions under Body System of Infections except for rare infections of Public Health interest will be considered listed

<sup>+</sup> - All adverse reactions under HLT of Rash will be considered listed

The following adverse events which have occurred in other indications and not described above have been reported (5%-10%) in patients treated with REVLIMID monotherapy for mantle cell lymphoma.

**General disorders and administration site conditions:** Chills  
**Musculoskeletal and connective tissue disorders:** Pain in extremity  
**Nervous system disorders:** Dysgeusia, headache, neuropathy peripheral  
**Infections and infestations:** Respiratory tract infection, sinusitis, nasopharyngitis  
**Skin and subcutaneous tissue disorders:** Dry skin, night sweats

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

**Respiratory, thoracic, and mediastinal disorders:** Chronic obstructive pulmonary disease  
**Infections and infestations:** *Clostridium difficile* colitis, sepsis  
**Neoplasms benign, malignant and unspecified (including cysts and polyps):** Basal cell carcinoma  
**Cardiac disorder:** Supraventricular tachycardia

## 6.2 Postmarketing Experience

The following adverse drug reactions have been identified from the worldwide post-marketing experience with REVLIMID. 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  
**Immune system disorders:** Angioedema, acute graft-versus-host disease (following allogeneic hematopoietic transplant)  
**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

## 7 DRUG INTERACTIONS

### 7.1 Digoxin

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

### 7.2 Concomitant Therapies That May Increase the Risk of Thrombosis

Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution after making a benefit-risk assessment in patients receiving REVLIMID [see *Warnings and Precautions (5.4)*].

### 7.3 Warfarin

Co-administration of multiple doses of REVLIMID (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 REVLIMID administration. It is not known whether there is an interaction between dexamethasone and warfarin. Close monitoring of PT and INR is recommended in patients with MM taking concomitant warfarin.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### *Pregnancy Exposure Registry*

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

#### *Risk Summary*

Based on the mechanism of action [see *Clinical Pharmacology (12.1)*] and findings from animal studies [see *Data*], REVLIMID 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)*].

REVLIMID is a thalidomide analogue. Thalidomide is a human teratogen, inducing a high frequency of severe and life-threatening birth defects such as amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia, micropinna, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented and mortality at or shortly after birth has been reported in about 40% of infants.

Lenalidomide caused thalidomide-type limb defects in monkey offspring. Lenalidomide crossed the placenta after administration to pregnant rabbits and pregnant rats [see *Data*]. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to a fetus.

If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Report any suspected fetal exposure to REVLIMID to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.

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%-4% and of miscarriage is 15%-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 20-40% of the maternal C<sub>max</sub>. 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 REVLIMID on the breastfed infant, or the effects of REVLIMID on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed infants from REVLIMID, advise women not to breastfeed during treatment with REVLIMID.

## **8.3 Females and Males of Reproductive Potential**

### Pregnancy Testing

REVLIMID 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 REVLIMID therapy and during therapy. Advise females of reproductive potential that they must avoid pregnancy 4 weeks before therapy, while taking REVLIMID, during dose interruptions and for at least 4 weeks after completing therapy.

Females of reproductive potential must have 2 negative pregnancy tests before initiating REVLIMID. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing REVLIMID. Once treatment has started and during dose interruptions, pregnancy testing for females of reproductive potential should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. REVLIMID treatment must be discontinued during this evaluation.

### Contraception

#### *Females*

Females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously: one highly effective form of contraception – tubal ligation, IUD, hormonal (birth control pills, injections, hormonal patches, vaginal rings, or implants), or partner's vasectomy, and 1 additional effective contraceptive method – male latex or synthetic condom, diaphragm, or cervical cap. Contraception must begin 4 weeks prior to initiating treatment with REVLIMID, during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of REVLIMID therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. Females of reproductive potential should be referred to a qualified provider of contraceptive methods, if needed.

#### *Males*

Lenalidomide is present in the semen of males who take REVLIMID. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID 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.

## **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 Maintenance Therapy:** Overall, 10% (106/1018) of patients were 65 years of age or older, while no patients were over 75 years of age. Grade 3 or 4 AEs were higher in the REVLIMID arm (more than 5% higher) in the patients 65 years of age or older versus younger patients. The frequency of Grade 3 or 4 AEs in the Blood and Lymphatic System Disorders were higher in the REVLIMID arm (more than 5% higher) in the patients 65 years of age or older versus younger patients. There were not a sufficient number of patients 65 years of age or older in REVLIMID maintenance studies who experienced either a serious AE, or discontinued therapy due to an AE to determine whether elderly patients respond relative to safety differently from younger patients.



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

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

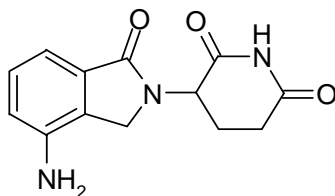
Adjust the starting dose of REVLIMID based on the creatinine clearance value and for patients on dialysis [see *Dosage and Administration* (2.4)].

## 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

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



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

The empirical formula for lenalidomide is C<sub>13</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub>, and the gram molecular weight is 259.3.

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

REVLIMID is available in 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg and 25 mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The 5 mg and 25 mg capsule shell contains gelatin, titanium dioxide and black ink. The 2.5 mg and 10 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink. The 15 mg capsule shell contains gelatin, FD&C blue #2, titanium dioxide and black ink. The 20 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Lenalidomide is an analogue of thalidomide with immunomodulatory, antiangiogenic, and antineoplastic properties. 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, mantle cell lymphoma, and del (5q) myelodysplastic syndromes *in vitro*. Lenalidomide causes a delay in tumor growth in some *in vivo* nonclinical hematopoietic tumor models including MM. Immunomodulatory properties of lenalidomide include increased number and activation of T cells and natural killer (NK) cells leading to direct and enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) via increased secretion of interleukin-2 and interferon-gamma, increased numbers of NKT cells, and inhibition of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. In MM cells, the combination of lenalidomide and dexamethasone synergizes the inhibition of cell proliferation and the induction of apoptosis.

## 12.2 Pharmacodynamics

### Cardiac Electrophysiology

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

## 12.3 Pharmacokinetics

### Absorption

Lenalidomide is rapidly absorbed following oral administration. Following single and multiple doses of REVLIMID in patients with MM or MDS, the maximum plasma concentrations occurred between 0.5 and 6 hours post-dose. The single and multiple dose pharmacokinetic disposition of lenalidomide is linear with AUC and  $C_{max}$  values increasing proportionally with dose. Multiple doses of REVLIMID at the recommended dosage does not result in drug accumulation.

Administration of a single 25 mg dose of REVLIMID with a high-fat meal in healthy subjects reduces the extent of absorption, with an approximate 20% decrease in AUC and 50% decrease in  $C_{max}$ . In the trials where the efficacy and safety were established for REVLIMID, the drug was administered without regard to food intake. REVLIMID can be administered with or without food.

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

### Distribution

In vitro [ $^{14}C$ ]-lenalidomide binding to plasma proteins is approximately 30%.

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

### 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 [ $^{14}C$ ]-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 REVLIMID. Three healthy subjects of similar age with normal renal function (CLcr > 80 mL/min) were also administered a single 25 mg dose of REVLIMID. 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 REVLIMID 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 REVLIMID (25 mg).

Co-administration of REVLIMID (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 REVLIMID (25 mg) did not significantly alter the pharmacokinetics of lenalidomide, temsirolimus, or sirolimus (metabolite of temsirolimus).

In vitro studies demonstrated that REVLIMID is a substrate of P-glycoprotein (P-gp). REVLIMID is not a substrate of human breast cancer resistance protein (BCRP), multidrug resistance protein (MRP) transporters MRP1, MRP2, or MRP3, organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptide 1B1 (OATP1B1), 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 REVLIMID 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 ( $\leq 75$  versus  $> 75$  years), stage (ISS Stages I and II versus Stage III), and country.

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

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

The primary efficacy endpoint, progression-free survival (PFS), was defined as the time from randomization to the first documentation of disease progression as determined by Independent Response Adjudication Committee (IRAC), based on International Myeloma Working Group [IMWG] criteria or death due to any cause, whichever occurred first during the study until the end of the PFS follow-up phase. For the efficacy analysis of all endpoints, the primary comparison was between Rd Continuous and MPT arms. The efficacy results are summarized in the table below. PFS was significantly longer with Rd Continuous than MPT: HR 0.72 (95% CI: 0.61-0.85  $p < 0.0001$ ). 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)**

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

CR = complete response; d = low-dose dexamethasone; HR = hazard ratio; IRAC = Independent Response Adjudication Committee; M = melphalan; NE = not estimable; OS = overall survival; P = prednisone; PFS = progression-free survival; PR = partial response; R = lenalidomide; Rd

Continuous = Rd given until documentation of progressive disease; Rd18 = Rd given for  $\leq 18$  cycles; T = thalidomide; VGPR = very good partial response; vs = versus.

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

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

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

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

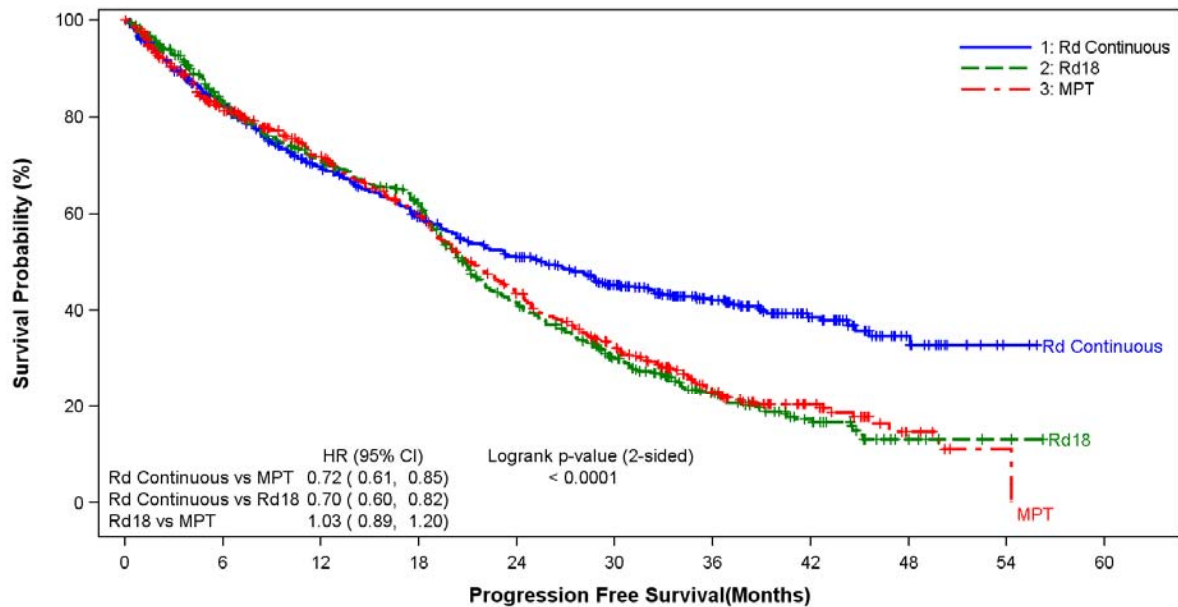
<sup>e</sup> Best assessment of response during the treatment phase of the study

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

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

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

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



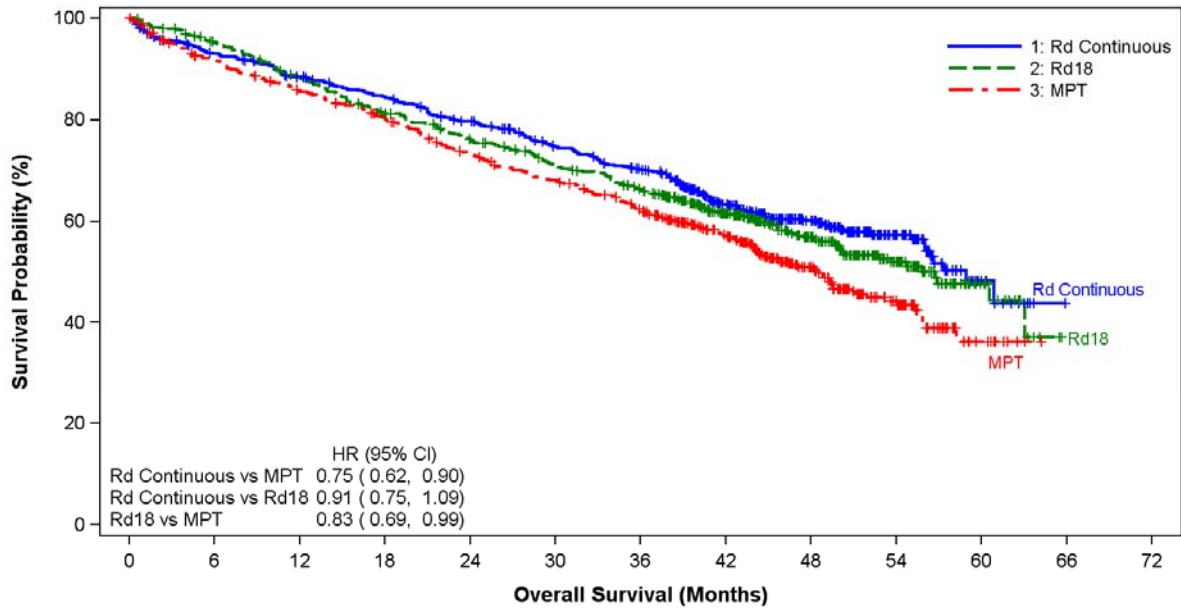
1	535	400	319	265	218	168	105	55	19	2	0
2	541	391	319	265	167	108	56	30	7	2	0
3	547	380	304	244	170	116	58	28	6	1	0

**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.

**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	13	0
2	541	505	465	425	394	362	329	238	146	72	18	0
3	547	484	448	418	375	347	310	230	130	58	10	0

**Number of Subjects at Risk**

OS Events: Rd Continuous=209/535 ( 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, Placebo-Controlled Clinical Trials - Maintenance Following Auto-HSCT:**

Two multicenter, randomized, double-blind, parallel group, placebo-controlled studies were conducted to evaluate the efficacy and safety of REVLIMID maintenance therapy in the treatment of MM patients after auto-HSCT. In Maintenance Study 1, patients between 18 and 70 years of age who had undergone induction therapy followed by auto-HSCT were eligible. Induction therapy must have occurred within 12 months. Within 90-100 days after auto-HSCT, patients with at least a stable disease response were randomized 1:1 to receive either REVLIMID or placebo maintenance. In Maintenance Study 2, patients aged < 65 years at diagnosis who had undergone induction therapy followed by auto-HSCT and had achieved at least a stable disease response at the time of hematologic recovery were eligible. Within 6 months after auto-HSCT, patients were randomized 1:1 to receive either REVLIMID or placebo maintenance. Patients eligible for both trials had to have CLcr ≥30 mL/minute.

In both studies, the REVLIMID maintenance dose was 10 mg once daily on days 1-28 of repeated 28-day cycles, could be increased to 15 mg once daily after 3 months in the absence of dose-limiting toxicity, and treatment was to be continued until disease progression or patient withdrawal for another reason. The dose was reduced, or treatment was temporarily interrupted or stopped, as needed to manage toxicity. A dose increase to 15 mg once daily occurred in 135 patients (58%) in Maintenance Study 1, and in 185 patients (60%) in Maintenance Study 2.

The demographics and disease-related baseline characteristics of the patients were similar across the two studies and reflected a typical MM population after auto-HSCT (see Table 13).

























- 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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RevPlyPI.021/MG.021 02/17

**MEDICATION GUIDE**  
REVLIMID<sup>®</sup> (rev-li-mid)  
(lenalidomide)  
capsules

**What is the most important information I should know about REVLIMID?**

Before you begin taking REVLIMID, you must read and agree to all of the instructions in the REVLIMID REMS<sup>®</sup> program. Before prescribing REVLIMID, your healthcare provider will explain the REVLIMID REMS program to you and have you sign the Patient-Physician Agreement Form.

REVLIMID may cause serious side effects including:

- **Possible birth defects (deformed babies) or death of an unborn baby.** Females who are pregnant or who plan to become pregnant must not take REVLIMID. **REVLIMID is similar to the medicine thalidomide (THALOMID<sup>®</sup>).** We know thalidomide can cause severe life-threatening birth defects. REVLIMID has not been tested in pregnant females. REVLIMID has harmed unborn animals in animal testing.

**Females must not get pregnant:**

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

**Females who can become pregnant:**

- Will have pregnancy tests weekly for 4 weeks, then every 4 weeks if your menstrual cycle is regular, or every 2 weeks if your menstrual cycle is irregular.
- If you miss your period or have unusual bleeding, you will need to have a pregnancy test and receive counseling.
- Must agree to use two acceptable forms of birth control at the same time, for at least 4 weeks before, while taking, during any breaks (interruptions) in your treatment, and for at least 4 weeks after stopping REVLIMID.
- 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 REVLIMID.
- If you had unprotected sex or if you think your birth control has failed, stop taking REVLIMID immediately and call your healthcare provider right away.

**If you become pregnant while taking REVLIMID, stop taking it right away and call your healthcare provider.** If your healthcare provider is not available, you can call Celgene Customer Care Center at 1-888-423-5436. Healthcare providers and patients should report all cases of pregnancy to:

- FDA MedWatch at 1-800-FDA-1088, and
- Celgene Corporation at 1-888-423-5436

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

**REVLIMID can pass into human semen:**

- Males, including those who have had a vasectomy, must always use a latex or synthetic condom during any sexual contact with a pregnant female or a female that can become pregnant while taking REVLIMID, during any breaks (interruptions) in your treatment with REVLIMID, and for up to 4 weeks after stopping REVLIMID.
- Do not have unprotected sexual contact with a female who is or could become pregnant. Tell your healthcare provider if you do have unprotected sexual contact with a female who is or could become pregnant.
- Do not donate sperm while taking REVLIMID, during any breaks (interruptions) in your treatment, and for 4 weeks after stopping REVLIMID. If a female becomes pregnant with your sperm, the

baby may be exposed to REVLIMID and may be born with birth defects.

**Men, if your female partner becomes pregnant, you should call your healthcare provider right away.**

- **Low white blood cells (neutropenia) and low platelets (thrombocytopenia).** REVLIMID causes low white blood cells and low platelets in most people. You may need a blood transfusion or certain medicines if your blood counts drop too low. Your healthcare provider should check your blood counts often especially during the first several months of treatment with REVLIMID, and then at least monthly. Tell your healthcare provider if you develop any bleeding or bruising, during treatment with REVLIMID.
- **Blood clots.** Blood clots in the arteries, veins, and lungs happen more often in people who take REVLIMID. This risk is even higher for people with multiple myeloma who take the medicine dexamethasone with REVLIMID. Heart attacks and strokes also happen more often in people who take REVLIMID with dexamethasone. To reduce this increased risk, most people who take REVLIMID will also take a blood thinner medicine.

Before taking REVLIMID, tell your healthcare provider:

- If you have had a blood clot in the past
- If you have high blood pressure, smoke, or if you have been told you have a high level of fat in your blood (hyperlipidemia)
- About all the medicines you take. Certain other medicines can also increase your risk for blood clots

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

- **Signs or symptoms of a blood clot in the lung, arm, or leg may include:** shortness of breath, chest pain, or arm or leg swelling
- **Signs or symptoms of a heart attack may include:** chest pain that may spread to the arms, neck, jaw, back, or stomach area (abdomen), feeling sweaty, shortness of breath, feeling sick or vomiting
- **Signs or symptoms of stroke may include:** sudden numbness or weakness, especially on one side of the body, severe headache or confusion, or problems with vision, speech, or balance

#### **What is REVLIMID?**

REVLIMID is a prescription medicine, used to treat people with:

- multiple myeloma (MM)
  - in combination with the medicine dexamethasone, or
  - as maintenance treatment after autologous hematopoietic stem cell transplantation (a type of stem cell transplant that uses your own stem cells)
- a condition called myelodysplastic syndromes (MDS). REVLIMID is for the type of MDS with a chromosome problem where part of chromosome 5 is missing. This type of MDS is known as deletion 5q MDS. People with this type of MDS may have low red blood cell counts that require treatment with blood transfusions.
- 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.

REVLIMID should not be used to treat people who have chronic lymphocytic leukemia (CLL) unless they are participants in a controlled clinical trial.

It is not known if REVLIMID is safe and effective in children.

#### **Who should not take REVLIMID?**

**Do not take REVLIMID if you:**

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

#### **What should I tell my healthcare provider before taking REVLIMID?**

**Before you take REVLIMID, 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
- are lactose intolerant. REVLIMID contains lactose.
- are breastfeeding. Do not breastfeed during treatment with REVLIMID. It is not known if REVLIMID passes into your breast milk and can harm your baby.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. REVLIMID and other medicines may affect each other, causing serious side effects. 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 REVLIMID?**

- Take REVLIMID exactly as prescribed and follow all the instructions of the REVLIMID REMS program
- Swallow REVLIMID capsules whole with water 1 time a day. **Do not open, break, or chew your capsules.**
- **REVLIMID may be taken with or without food.**
- Take REVLIMID at about the same time each day.
- Do not open or break REVLIMID capsules or handle them any more than needed.
  - If powder from the REVLIMID capsule comes in contact with your skin, wash the skin right away with soap and water.
  - If powder from the REVLIMID capsule comes in contact with the inside of your eyes, nose, or mouth, flush well with water.
- If you miss a dose of REVLIMID and it has been less than 12 hours since your regular time, take it as soon as you remember. If it has been more than 12 hours, just skip your missed dose. Do not take 2 doses at the same time.
- If you take too much REVLIMID, call your healthcare provider right away.

#### **What should I avoid while taking REVLIMID?**

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

#### **What are the possible side effects of REVLIMID?**

**REVLIMID can cause serious side effects, including:**

- See “What is the most important information I should know about REVLIMID?”
- **Increased risk of death in people who have chronic lymphocytic leukemia (CLL).** People with CLL who take REVLIMID have an increased risk of death compared with people who take the medicine chlorambucil. REVLIMID may cause you to have serious heart problems that can lead to death, including atrial fibrillation, heart attack, or heart failure. You should not take REVLIMID if you have CLL unless you are participating in a controlled clinical trial.
- **Risk of new cancers (malignancies).** An increase in new (second) cancers has happened in patients who received REVLIMID 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 REVLIMID. Your healthcare provider will check you for new cancers during your treatment with REVLIMID.
- **Severe liver problems, including liver failure and death.** Your healthcare provider should do blood tests to check your liver function during your treatment with REVLIMID. Tell your healthcare provider right away if you develop any of the following symptoms of liver problems:
  - yellowing of your skin or the white part of your eyes (jaundice)
  - pain on the upper right side of your stomach area (abdomen)

- dark or brown (tea-colored) urine
- bleeding or bruising more easily than normal
- feeling very tired
- **Serious allergic reactions and serious skin reactions** can happen with REVLIMID and may cause death. Call your healthcare provider right away if you develop any of these signs or symptoms of a serious allergic reaction or serious skin reaction during treatment with REVLIMID:
  - swelling of your face, eyes, lips, tongue, throat
  - skin rash, hives, or peeling of your skin
  - blisters
  - trouble swallowing
  - trouble breathing
- **Tumor lysis syndrome (TLS).** TLS is caused by the fast breakdown of cancer cells. TLS can cause kidney failure and the need for dialysis treatment, abnormal heart rhythm, seizure and sometimes death. Your healthcare provider may do blood tests to check you for TLS.
- **Worsening of your tumor (tumor flare reaction).** Tell your healthcare provider if you get any of these symptoms of tumor flare reaction while taking REVLIMID: tender swollen lymph nodes, low grade fever, pain, or rash.

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

- **Thyroid problems.** Your healthcare provider may check your thyroid function before you start taking REVLIMID and during treatment with REVLIMID.

The most common side effects of REVLIMID include:

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

These are not all the possible side effects of REVLIMID.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

#### How should I store REVLIMID?

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

**Keep REVLIMID and all medicines out of the reach of children.**

#### General information about the safe and effective use of REVLIMID

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not take REVLIMID for conditions for which it was not prescribed. Do not give REVLIMID to other people, even if they have the same symptoms you have. It may harm them and may cause birth defects.

If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about REVLIMID that is written for health professionals.

#### What are the ingredients in REVLIMID?

**Active ingredient:** lenalidomide

**Inactive ingredients:** lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

The 5 mg and 25 mg capsule shell contains gelatin, titanium dioxide and black ink.

The 2.5 and 10 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink.

The 15 mg capsule shell contains gelatin, FD&C blue #2, titanium dioxide and black ink.

The 20 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink.

Manufactured for: Celgene Corporation, Summit, NJ 07901

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For more information, call 1-888-423-5436 or go to [www.CelgeneRiskManagement.com](http://www.CelgeneRiskManagement.com).

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

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