Table 5: All Adverse Reactions in ≥5% and Grade 3/4 Adverse Reactions in ≥1% of Patients with MM 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)	94 (43)	133 (59)	73 (33)	178 (61)	33 (12)	158 (54)	21 (8)
Thrombocytopenia [c %]	162 (72)	101 (46)	84 (38)	67 (30)	69 (24)	29 (10)	38 (13)	8 (3)
Leukopenia [c]	51 (23)	25 (11)	45 (20)	22 (10)	93 (32)	21 (8)	71 (24)	5 (2)
Anemia	47 (21)	27 (12)	23 (10)	18 (8)	26 (9)	15 (5)	11 (4)	3 (1)
Lymphopenia	40 (18)	29 (13)	37 (17)	26 (12)	13 (4)	3 (1)	11 (4)	< 1%
Pancytopenia [c d %]	< 1%	0 (0)	0 (0)	0 (0)	12 (4)	< 1%	7 (2)	< 1%
Febrile neutropenia [c]	39 (17)	34 (15)	39 (17)	34 (15)	7 (2)	< 1%	5 (2)	< 1%
Infections and infestations[#]								
Upper respiratory tract infection [e]	60 (27)	35 (16)	7 (3)	9 (4)	32 (11)	18 (6)	< 1%	0 (0)
Neutropenic infection	40 (18)	19 (9)	27 (12)	14 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Pneumonias* [c %]	31 (14)	15 (7)	23 (10)	7 (3)	50 (17)	13 (5)	27 (9)	5 (2)
Bronchitis [c]	10 (4)	9 (4)	< 1%	5 (2)	139 (47)	104 (37)	4 (1)	< 1%
Nasopharyngitis [e]	5 (2)	< 1%	0 (0)	0 (0)	102 (35)	84 (30)	< 1%	0 (0)
Gastroenteritis [c]	0 (0)	0 (0)	0 (0)	0 (0)	66 (23)	55 (20)	6 (2)	0 (0)
Rhinitis [e]	< 1%	0 (0)	0 (0)	0 (0)	44 (15)	19 (7)	0 (0)	0 (0)
Sinusitis [e]	8 (4)	3 (1)	0 (0)	0 (0)	41 (14)	26 (9)	0 (0)	< 1%
Influenza [c]	8 (4)	5 (2)	< 1%	< 1%	39 (13)	19 (7)	3 (1)	0 (0)
Lung infection [c]	21 (9)	< 1%	19 (8)	< 1%	9 (3)	4 (1)	< 1%	0 (0)
Lower respiratory tract infection [e]	13 (6)	5 (2)	6 (3)	4 (2)	4 (1)	4 (1)	0 (0)	< 1%
Infection [c]	12 (5)	6 (3)	9 (4)	5 (2)	17 (6)	5 (2)	0 (0)	0 (0)
Urinary tract infection [c d e]	9 (4)	5 (2)	4 (2)	4 (2)	22 (8)	17 (6)	< 1%	0 (0)
Lower respiratory tract infection bacterial [d]	6 (3)	< 1%	4 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Bacteremia [d]	5 (2)	0 (0)	4 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Herpes zoster [c d]	11 (5)	10 (5)	3 (1)	< 1%	29 (10)	25 (9)	6 (2)	< 1%
Sepsis* [c d @]	< 1%	< 1%	0 (0)	0 (0)	6 (2)	< 1%	4 (1)	< 1%
Gastrointestinal disorders								
Diarrhea	122 (54)	83 (38)	22 (10)	17 (8)	114 (39)	34 (12)	7 (2)	0 (0)
Nausea [e]	33 (15)	22 (10)	16 (7)	10 (5)	31 (11)	28 (10)	0 (0)	0 (0)
Vomiting	17 (8)	12 (5)	8 (4)	5 (2)	16 (5)	15 (5)	< 1%	0 (0)
Constipation [e]	12 (5)	8 (4)	0 (0)	0 (0)	37 (13)	25 (9)	< 1%	0 (0)
Abdominal pain [e]	8 (4)	7 (3)	< 1%	4 (2)	31 (11)	15 (5)	< 1%	< 1%
Abdominal pain upper [e]	0 (0)	0 (0)	0 (0)	0 (0)	20 (7)	12 (4)	< 1%	0 (0)
General disorders and administration site conditions								
Asthenia	0 (0)	< 1%	0 (0)	0 (0)	87 (30)	53 (19)	10 (3)	< 1%
Fatigue	51 (23)	30 (14)	21 (9)	9 (4)	31 (11)	15 (5)	3 (1)	0 (0)
Pyrexia [e]	17 (8)	10 (5)	< 1%	< 1%	60 (20)	26 (9)	< 1%	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 (%)
Skin and subcutaneous tissue disorders								
Dry skin [e]	9 (4)	4 (2)	0 (0)	0 (0)	31 (11)	21 (8)	0 (0)	0 (0)
Rash	71 (32)	48 (22)	11 (5)	5 (2)	22 (8)	17 (6)	3 (1)	0 (0)
Pruritus	9 (4)	4 (2)	3 (1)	0 (0)	21 (7)	25 (9)	< 1%	0 (0)
Nervous system disorders								
Paresthesia [e]	< 1%	0 (0)	0 (0)	0 (0)	39 (13)	30 (11)	< 1%	0 (0)
Peripheral neuropathy* [e]	34 (15)	30 (14)	8 (4)	8 (4)	29 (10)	15 (5)	4 (1)	< 1%
Headache [d]	11 (5)	8 (4)	5 (2)	< 1%	25 (9)	21 (8)	0 (0)	0 (0)
Investigations								
Alanine aminotransferase increased	16 (7)	3 (1)	8 (4)	0 (0)	5 (2)	5 (2)	0 (0)	< 1%
Aspartate aminotransferase increased [d]	13 (6)	5 (2)	6 (3)	0 (0)	< 1%	5 (2)	0 (0)	0 (0)
Metabolism and nutrition disorders								
Hypokalemia	24 (11)	13 (6)	16 (7)	12 (5)	12 (4)	< 1%	< 1%	0 (0)
Dehydration	9 (4)	5 (2)	7 (3)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Hypophosphatemia [d]	16 (7)	15 (7)	13 (6)	14 (6)	0 (0)	< 1%	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders								
Muscle spasms [e]	0 (0)	< 1%	0 (0)	0 (0)	98 (33)	43 (15)	< 1%	0 (0)
Myalgia [e]	7 (3)	8 (4)	3 (1)	5 (2)	19 (6)	12 (4)	< 1%	< 1%
Musculoskeletal pain [e]	< 1%	< 1%	0 (0)	0 (0)	19 (6)	11 (44)	0 (0)	0 (0)
Hepatobiliary disorders								
Hyperbilirubinemia [e]	34 (15)	19 (9)	4 (2)	< 1%	4 (1)	< 1%	< 1%	0 (0)
Respiratory, thoracic and mediastinal disorders								
Cough [e]	23 (10)	12 (5)	3 (1)	< 1%	80 (27)	56 (20)	0 (0)	0 (0)
Dyspnea [c e]	15 (7)	9 (4)	8 (4)	4 (2)	17 (6)	9 (3)	< 1%	0 (0)
Rhinorrhea [e]	0 (0)	3 (1)	0 (0)	0 (0)	15 (5)	6 (2)	0 (0)	0 (0)
Pulmonary embolism [c d e]	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	0 (0)	< 1%	0 (0)
Vascular disorders								
Deep vein thrombosis* [c d %]	8 (4)	< 1%	5 (2)	< 1%	7 (2)	< 1%	4 (1)	< 1%
Neoplasms benign, malignant and unspecified (including cysts and polyps)								
Myelodysplastic syndrome [c d e]	5 (2)	0 (0)	< 1%	0 (0)	3 (1)	0 (0)	< 1%	0 (0)

Note: Adverse Events (AEs) are coded to Body System /Adverse Reaction using MedDRA v15.1. A subject with multiple occurrences of an adverse reaction is counted only once under the applicable Body System/Adverse Reaction.

[a] All treatment-emergent AEs in at least 5% of patients in the REVLIMID 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 REVLIMID 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 REVLIMID 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 with MM 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)	22 (6)
Anemia[@]	111 (31)	83 (24)
Thrombocytopenia[@]	76 (22)	37 (11)
Leukopenia	28 (8)	4 (1)
Lymphopenia	19 (5)	5 (1)
General disorders and administration site conditions		
Fatigue	155 (44)	146 (42)
Pyrexia	97 (27)	82 (23)
Peripheral edema	93 (26)	74 (21)
Chest pain	29 (8)	20 (6)
Lethargy	24 (7)	8 (2)
Gastrointestinal disorders		
Constipation	143 (41)	74 (21)
Diarrhea[@]	136 (39)	96 (27)
Nausea[@]	92 (26)	75 (21)
Vomiting[@]	43 (12)	33 (9)
Abdominal pain[@]	35 (10)	22 (6)
Dry mouth	25 (7)	13 (4)
Musculoskeletal and connective tissue disorders		
Muscle cramp	118 (33)	74 (21)
Back pain	91 (26)	65 (19)
Bone pain	48 (14)	39 (11)
Pain in limb	42 (12)	32 (9)
Nervous system disorders		
Dizziness	82 (23)	59 (17)
Tremor	75 (21)	26 (7)
Dysgeusia	54 (15)	34 (10)
Hypoesthesia	36 (10)	25 (7)
Neuropathy[a]	23 (7)	13 (4)
Respiratory, thoracic and mediastinal disorders		
Dyspnea	83 (24)	60 (17)
Nasopharyngitis	62 (18)	31 (9)
Pharyngitis	48 (14)	33 (9)
Bronchitis	40 (11)	30 (9)
Infections[b] and infestations		

Body System Adverse Reaction	**REVLIMID/Dex** **(N=353)** **n (%)**	**Placebo/Dex** **(N=350)** **n (%)**
Upper respiratory tract infection	87 (25)	55 (16)
Pneumonia[@]	48 (14)	29 (8)
Urinary tract infection	30 (8)	19 (5)
Sinusitis	26 (7)	16 (5)
Skin and subcutaneous system disorders		
Rash[c]	75 (21)	33 (9)
Sweating increased	35 (10)	25 (7)
Dry skin	33 (9)	14 (4)
Pruritus	27 (8)	18 (5)
Metabolism and nutrition disorders		
Anorexia	55 (16)	34 (10)
Hypokalemia	48 (14)	21 (6)
Hypocalcemia	31 (9)	10 (3)
Appetite decreased	24 (7)	14 (4)
Dehydration	23 (7)	15 (4)
Hypomagnesemia	24 (7)	10 (3)
Investigations		
Weight decreased	69 (20)	52 (15)
Eye disorders		
Blurred vision	61 (17)	40 (11)
Vascular disorders		
Deep vein thrombosis[%]	33 (9)	15 (4)
Hypertension	28 (8)	20 (6)
Hypotension	25 (7)	15 (4)

Table 7: Grade 3/4 Adverse Reactions Reported in ≥2% Patients and with a ≥1% Difference in Proportion of Patients with MM 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)	12 (3)
Thrombocytopenia[@]	43 (12)	22 (6)
Anemia[@]	35 (10)	20 (6)
Leukopenia	14 (4)	< 1%
Lymphopenia	10 (3)	4 (1)
Febrile neutropenia[%]	8 (2)	0 (0)
General disorders and administration site conditions		
Fatigue	23 (7)	17 (5)
Vascular disorders		
Deep vein thrombosis[%]	29 (8)	12 (3)
Infections and infestations		
Pneumonia[@]	30 (8)	19 (5)
Urinary tract infection	5 (1)	< 1%
Metabolism and nutrition disorders		
Hypokalemia	17 (5)	5 (1)
Hypocalcemia	13 (4)	6 (2)
Hypophosphatemia	9 (3)	0 (0)
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism[@]	14 (4)	< 1%
Respiratory distress[@]	4 (1)	0 (0)

Body System Adverse Reaction	**REVLIMID/Dex** **(N=353)** **n (%)**	**Placebo/Dex** **(N=350)** **n (%)**
Musculoskeletal and connective tissue disorders		
Muscle weakness	20 (6)	10 (3)
Gastrointestinal disorders		
Diarrhea[@]	11 (3)	4 (1)
Constipation	7 (2)	< 1%
Nausea[@]	6 (2)	< 1%
Cardiac disorders		
Atrial fibrillation[@]	13 (4)	4 (1)
Tachycardia	6 (2)	< 1%
Cardiac failure congestive[@]	5 (1)	< 1%
Nervous system disorders		
Syncope	10 (3)	< 1%
Dizziness	7 (2)	< 1%
Eye disorders		
Cataract	6 (2)	< 1%
Cataract unilateral	5 (1)	0 (0)
Psychiatric disorder		
Depression	10 (3)	6 (2)

Table 8: Serious Adverse Reactions Reported in ≥1% Patients and with a ≥1% Difference in Proportion of Patients with MM 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		
Febrile neutropenia[%]	6 (2)	0 (0)
Vascular disorders		
Deep vein thrombosis[%]	26 (7)	11 (3)
Infections and infestations		
Pneumonia[@]	33 (9)	21 (6)
Respiratory, thoracic, and mediastinal disorders		
Pulmonary embolism[@]	13 (4)	< 1%
Cardiac disorders		
Atrial fibrillation[@]	11 (3)	< 1%
Cardiac failure congestive[@]	5 (1)	0 (0)
Nervous system disorders		
Cerebrovascular accident[@]	7 (2)	< 1%
Gastrointestinal disorders		
Diarrhea [@]	6 (2)	< 1%
Musculoskeletal and connective tissue disorders		
Bone pain	4 (1)	0 (0)

For Tables 6, 7 and 8 above:
[@] - adverse reactions in which at least one resulted in a fatal outcome.
[%] - adverse reactions in which at least one was considered to be life threatening (if the outcome of the reaction was death, it is included with death cases).

Median duration of exposure among patients treated with 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 ≥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 reaction was reported in all of the 148 patients who were treated with the 10 mg starting dose of REVLIMID. The most frequently reported adverse reactions were related to blood and lymphatic system disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders, and general disorders and administrative site conditions.

Thrombocytopenia (61.5%; 91/148) and neutropenia (58.8%; 87/148) were the most frequently reported adverse reactions. The next most common adverse reactions observed were diarrhea (48.6%; 72/148), pruritus (41.9%; 62/148), rash (35.8%; 53/148) and fatigue (31.1%; 46/148). Table 9 summarizes the adverse reactions that were reported in ≥ 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 reactions that are drug-related and those that reflect the patient's underlying disease.

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

Body System Adverse Reaction [a]	10 mg Overall (N=148)	
Patients with at least one adverse reaction	148	(100)
Blood and Lymphatic System Disorders		
Thrombocytopenia	91	(61)
Neutropenia	87	(59)
Anemia	17	(11)
Leukopenia	12	(8)
Febrile Neutropenia	8	(5)
Skin and Subcutaneous Tissue Disorders		
Pruritus	62	(42)
Rash	53	(36)
Dry Skin	21	(14)
Contusion	12	(8)
Night Sweats	12	(8)
Sweating Increased	10	(7)
Ecchymosis	8	(5)

Body System Adverse Reaction [a]	10 mg Overall (N=148)	
Erythema	8	(5)
Gastrointestinal Disorders		
Diarrhea	72	(49)
Constipation	35	(24)
Nausea	35	(24)
Abdominal Pain	18	(12)
Vomiting	15	(10)
Abdominal Pain Upper	12	(8)
Dry Mouth	10	(7)
Loose Stools	9	(6)
Respiratory, Thoracic and Mediastinal Disorders		
Nasopharyngitis	34	(23)
Cough	29	(20)
Dyspnea	25	(17)
Pharyngitis	23	(16)
Epistaxis	22	(15)
Dyspnea Exertional	10	(7)
Rhinitis	10	(7)
Bronchitis	9	(6)
General Disorders and Administration Site Conditions		
Fatigue	46	(31)
Pyrexia	31	(21)
Edema Peripheral	30	(20)
Asthenia	22	(15)
Edema	15	(10)
Pain	10	(7)
Rigors	9	(6)
Chest Pain	8	(5)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	32	(22)
Back Pain	31	(21)
Muscle Cramp	27	(18)
Pain in Limb	16	(11)
Myalgia	13	(9)
Peripheral Swelling	12	(8)
Nervous System Disorders		
Dizziness	29	(20)
Headache	29	(20)
Hypoesthesia	10	(7)
Dysgeusia	9	(6)
Peripheral Neuropathy	8	(5)
Infections and Infestations		
Upper Respiratory Tract Infection	22	(15)
Pneumonia	17	(11)
Urinary Tract Infection	16	(11)
Sinusitis	12	(8)
Cellulitis	8	(5)
Metabolism and Nutrition Disorders		
Hypokalemia	16	(11)
Anorexia	15	(10)
Hypomagnesemia	9	(6)
Investigations		
Alanine Aminotransferase Increased	12	(8)
Psychiatric Disorders		
Insomnia	15	(10)
Depression	8	(5)
Renal and Urinary Disorders		
Dysuria	10	(7)
Vascular Disorders		
Hypertension	9	(6)
Endocrine Disorders		
Acquired Hypothyroidism	10	(7)
Cardiac Disorders		
Palpitations	8	(5)

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

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

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

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

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

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

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

Ear and labyrinth disorders: vertigo

Endocrine disorders: Basedow's disease

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

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

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

Immune system disorders: hypersensitivity

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

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

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

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

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

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

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

Psychiatric disorders: confusional state

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

Reproductive system and breast disorders: pelvic pain

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

Skin and subcutaneous tissue disorders: acute febrile neutrophilic dermatosis

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

Mantle Cell Lymphoma:

In the MCL trial, a total of 134 patients received at least 1 dose of 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 reactions, and 51 patients (38%) underwent at least one dose reduction due to adverse reactions. Twenty-six patients (19%) discontinued treatment due to adverse reactions.

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

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

Body System Adverse Reaction	**All Adverse Reactions[1] (N=134) n (%)**	**Grade 3/4 Adverse Reactions[2] (N=134) n (%)**
Dyspnea[$]	24 (18)	8 (6)
Pleural Effusion	10 (7)	2 (1)
Hypoxia	3 (2)	2 (1)
Pulmonary embolism	3 (2)	2 (1)
Respiratory distress[$]	2 (1)	2 (1)
Oropharyngeal pain	13 (10)	0
Infections and infestations		
Pneumonia[@ $]	19 (14)	12 (9)
Upper respiratory tract infection	17 (13)	0
Cellulitis[$]	3 (2)	2 (1)
Bacteremia[$]	2 (1)	2 (1)
Staphylococcal sepsis[$]	2 (1)	2 (1)
Urinary tract infection[$]	5 (4)	2 (1)
Skin and subcutaneous tissue disorders		
Rash [+]	30 (22)	2 (1)
Pruritus	23 (17)	1 (<1)
Blood and lymphatic system disorders		
Neutropenia	65 (49)	58 (43)
Thrombocytopenia[% $]	48 (36)	37 (28)
Anemia[$]	41 (31)	15 (11)
Leukopenia[$]	20 (15)	9 (7)
Lymphopenia	10 (7)	5 (4)
Febrile neutropenia[$]	8 (6)	8 (6)
Metabolism and nutrition disorders		
Decreased appetite	19 (14)	1 (<1)
Hypokalemia	17 (13)	3 (2)
Dehydration[$]	10 (7)	4 (3)
Hypocalcemia	4 (3)	2 (1)
Hyponatremia	3 (2)	3 (2)
Renal and urinary disorders		
Renal failure[$]	5 (4)	2 (1)
Vascular disorders		
Hypotension[@ $]	9 (7)	4 (3)
Deep vein thrombosis[$]	5 (4)	5 (4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Tumor flare	13 (10)	0
Squamous cell carcinoma of skin[$]	4 (3)	4 (3)
Investigations		
Weight decreased	17 (13)	0

[1]-MCL trial AEs – All treatment emergent AEs with ≥10% of subjects.
[2]-MCL trial Grade 3/4 AEs – All treatment-emergent Grade 3/4 AEs in 2 or more subjects.
[$]-MCL trial Serious AEs – All treatment-emergent SAEs in 2 or more subjects.
[@] - Adverse reactions where at least one resulted in a fatal outcome.
[%] - Adverse reactions where at least one was considered to be Life Threatening (if the outcome of the event was death, it is included with death cases).
[#] - All adverse reactions under Body System of Infections except for rare infections of Public Health interest will be considered listed.
[+] - All adverse reactions under HLT of Rash will be considered listed.

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 adverse reaction categories (eg, all adverse reactions, grade 3/4 adverse reactions, serious adverse reactions) was higher in older (> 75 years of age) than in younger (≤ 75 years of age) subjects. Grade 3 or 4 adverse reactions in the General Disorders and Administration Site Conditions body system were consistently reported at a higher frequency (with a difference of at least 5%) in older subjects than in younger subjects across all treatment arms. Grade 3 or 4 adverse reactions in the Infections and Infestations, Cardiac Disorders (including cardiac failure and congestive cardiac failure), Skin and Subcutaneous Tissue Disorders, and Renal and Urinary Disorders (including renal failure) body systems were also reported slightly, but consistently, more frequently (<5% difference), in older subjects than in younger subjects across all treatment arms. For other body systems (e.g., Blood and Lymphatic System Disorders, Infections and Infestations, Cardiac Disorders, Vascular Disorders), there was a less consistent trend for increased frequency of grade 3/4 adverse reactions in older vs younger subjects across all treatment arms Serious adverse reactions were generally reported at a higher frequency in the older subjects than in the younger subjects across all treatment arms.

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

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

FL or MZL in Combination: Overall, 48% (282/590) of patients were 65 years of age or older, while 14% (82/590) of patients were over 75 years of age. The overall frequency of adverse reactions was similar in patients 65 years of age or older and younger patients for both studies pooled (98%). Grade 3 or 4 adverse reactions were higher in the REVLIMID arm (more than 5% higher) in the patients 65 years of age or older versus younger patients (71% versus 59%). The frequency of Grade 3 or 4 adverse reactions were higher in the REVLIMID arm (more than 5% higher) in the patients 65 years of age or older versus younger patients in the Blood and Lymphatic System Disorders (47% versus 40%) and Infections and Infestations (16% versus 11%). Serious adverse reactions were higher in the REVLIMID arm (more than 5% higher) in the patients 65 years of age or older versus younger patients (37% versus 18%). The frequency of serious adverse reactions were higher in the REVLIMID arm (more than 5% higher) in the patients 65 years of age or older versus younger patients in Infections and Infestations (15% versus 6%).

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

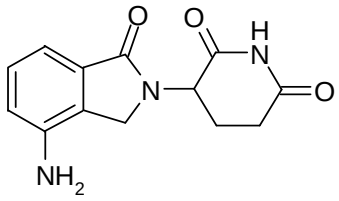
Adjust the starting dose of REVLIMID based on the creatinine clearance value and for patients on dialysis *[see Dosage and Administration (2.5)]*.

10 OVERDOSAGE

There is no specific experience in the management of REVLIMID overdose in patients with MM, MDS, MCL, FL, or MZL. 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-2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:



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

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

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

REVLIMID is available in 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, follicular lymphoma and marginal zone lymphoma *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. The combination of lenalidomide and rituximab increases ADCC and direct tumor apoptosis in follicular lymphoma cells and increases ADCC in marginal zone lymphoma cells compared to rituximab alone *in vitro*.

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 (2.5)]*.

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 Cmax 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 (≤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% ≥ 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 13: Overview of Efficacy Results – Study MM-020 (Intent-to-treat Population)

	Rd Continuous (N = 535)	**Rd18 (N = 541)**	**MPT (N = 547)**
PFS – IRAC (months)[g]			
Number of PFS events	278 (52)	348 (64.3)	334 (61.1)
Median[a] PFS time, months (95% CI)[b]	25.5 (20.7, 29.4)	20.7 (19.4, 22)	21.2 (19.3, 23.2)
HR [95% CI][c]; p-value[d]			
Rd Continuous vs MPT	0.72 (0.61, 0.85); <0.0001		
Rd Continuous vs Rd18	0.70 (0.60, 0.82)		
Rd18 vs MPT	1.03 (0.89, 1.20)		
Overall Survival (months)[h]			
Number of Death events	208 (38.9)	228 (42.1)	261 (47.7)
Median[a] OS time, months (95% CI)[b]	58.9 (56, NE)[f]	56.7 (50.1, NE)	48.5 (44.2, 52)
HR [95% CI][c]			
Rd Continuous vs MPT	0.75 (0.62, 0.90)		
Rd Continuous vs Rd18	0.91 (0.75, 1.09)		
Rd18 vs MPT	0.83 (0.69, 0.99)		
Response Rate[e] – IRAC, n (%)[g]			
CR	81 (15.1)	77 (14.2)	51 (9.3)
VGPR	152 (28.4)	154 (28.5)	103 (18.8)
PR	169 (31.6)	166 (30.7)	187 (34.2)
Overall response: CR, VGPR, or PR	402 (75.1)	397 (73.4)	341 (62.3)

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

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

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

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

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

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

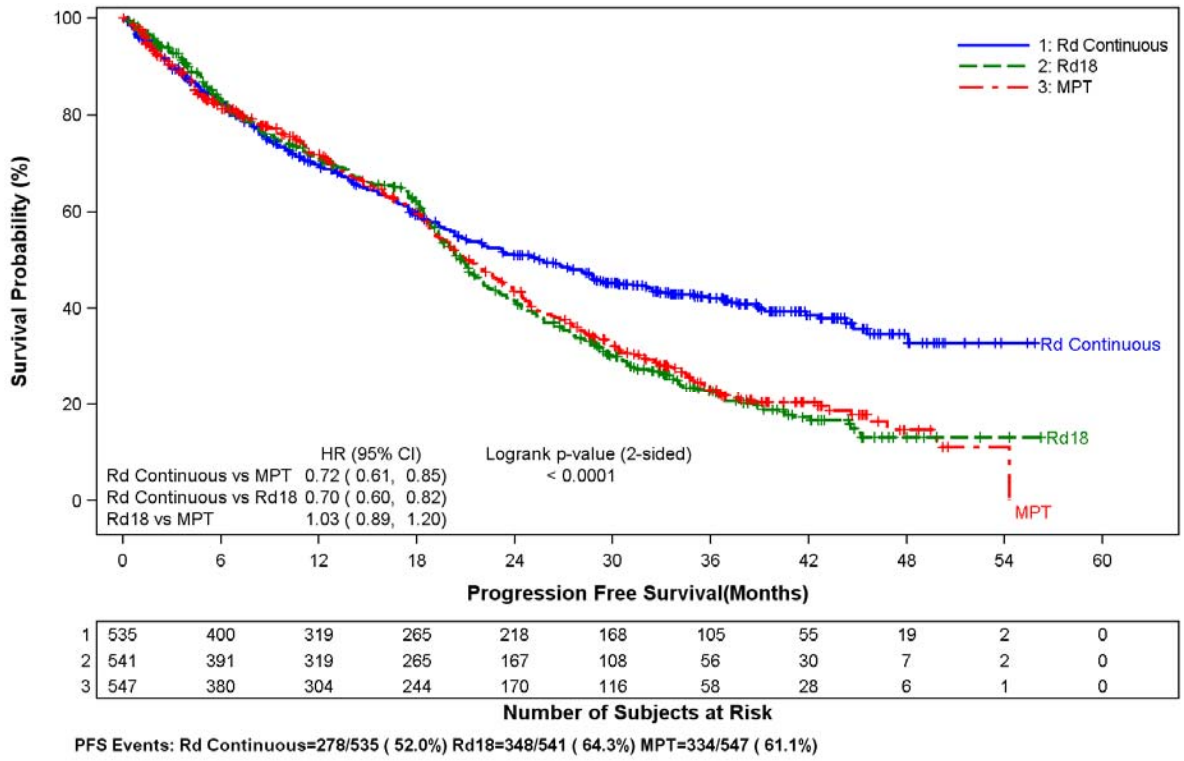
[e] Best assessment of response during the treatment phase of the study.

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

[g] Data cutoff date = 24 May 2013.

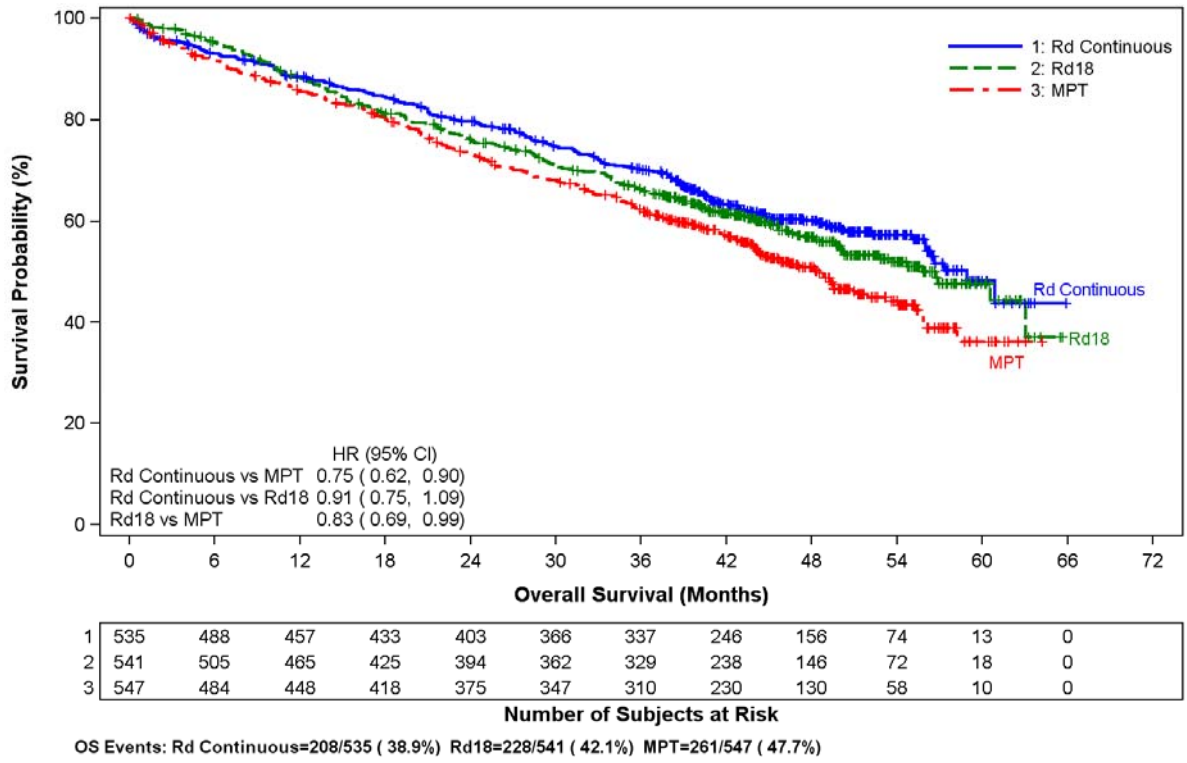
[h] Data cutoff date = 3 March 2014.

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



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

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



CI = confidence interval; d = low-dose dexamethasone; HR = hazard ratio; M = melphalan; P = prednisone; R = REVLIMID; 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 14).

Table 14: Baseline Demographic and Disease-Related Characteristics – MM Maintenance Studies 1 and 2

	Maintenance Study 1		Maintenance Study 2	
	REVLIMID N = 231	**Placebo** N = 229	**REVLIMID** N = 307	**Placebo** N = 307
Age (years)				
Median	58	58	57.5	58.1
(Min, max)	(29, 71)	(39, 71)	(22.7, 68.3)	(32.3, 67)
Sex, n (%)				
Male	121 (52)	129 (56)	169 (55)	181 (59)
Female	110 (48)	100 (44)	138 (45)	126 (41)
ISS Stage at Diagnosis, n (%)				
Stage I or II	120 (52)	131 (57)	232 (76)	250 (81)
Stage I	62 (27)	85 (37)	128 (42)	143 (47)
Stage II	58 (25)	46 (20)	104 (34)	107 (35)
Stage III	39 (17)	35 (15)	66 (21)	46 (15)
Missing	72 (31)	63 (28)	9 (3)	11 (4)
CrCl at Post-auto-HSCT, n (%)				
< 50 mL/min	23 (10)	16 (7)	10 (3)	9 (3)
≥ 50 mL/min	201 (87)	204 (89)	178 (58)	200 (65)
Missing	7 (3)	9 (4)	119 (39)	98 (32)

Data cutoff date = 1 March 2015.

The major efficacy endpoint of both studies was PFS defined from randomization to the date of progression or death, whichever occurred first; the individual studies were not powered for an overall survival endpoint. Both studies were unblinded upon the recommendations of their respective data monitoring committees and after surpassing the respective thresholds for preplanned interim analyses of PFS. After unblinding, patients continued to be followed as before. Patients in the placebo arm of Maintenance Study 1 were allowed to cross over to receive REVLIMID before disease progression (76 patients [33%] crossed over to REVLIMID); patients in Maintenance Study 2 were not recommended to cross over. The efficacy results are summarized in the following table. In both studies, the primary analysis of PFS at unblinding was significantly longer with REVLIMID compared to placebo: Maintenance Study 1 HR 0.38 (95% CI: 0.27-0.54 p <0.001) and Maintenance Study 2 HR 0.50 (95% CI: 0.39-0.64 p <0.001). For both studies, PFS was updated with a cutoff date of 1 March 2015 as shown in the table and the following Kaplan Meier graphs. With longer follow-up (median 72.4 and 86.0 months, respectively), the updated PFS analyses for both studies continue to show a PFS advantage for REVLIMID compared to placebo: Maintenance Study 1 HR 0.38 (95% CI: 0.28-0.50) with median PFS of 68.6 months and Maintenance Study 2 HR 0.53 (95% CI: 0.44-0.64) with median PFS of 46.3 months.

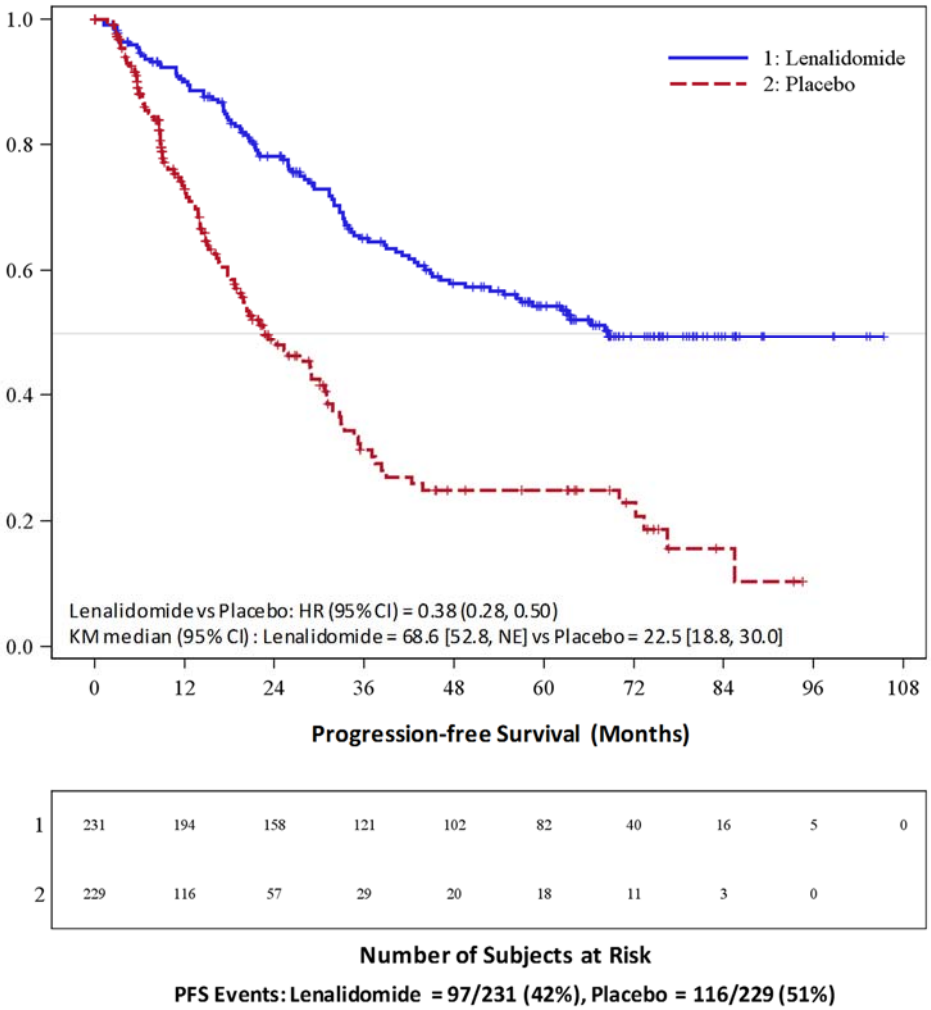
Descriptive analysis of OS data with a cutoff date of 1 February 2016 are provided in Table 15. Median follow-up time was 81.6 and 96.7 months for Maintenance Study 1 and Maintenance Study 2, respectively. Median OS was 111.0 and 84.2 months for REVLIMID and placebo, respectively, for Maintenance Study 1, and 105.9 and 88.1 months, for REVLIMID and placebo, respectively, for Maintenance Study 2.

Table 15: Progression-free Survival and Overall Survival from Randomization in MM Maintenance Studies 1 and 2 (ITT Post-Auto-HSCT Population)

	Maintenance Study 1		Maintenance Study 2	
	REVLIMID N = 231	**Placebo N = 229**	**REVLIMID N = 307**	**Placebo N = 307**
PFS at Unblinding				
PFS Events n (%)	46 (20)	98 (43)	103 (34)	160 (52)
Median in months [95% CI]	33.9 [NE, NE]	19 [16.2, 25.6]	41.2 [38.3, NE]	23.0 [21.2, 28.0]
Hazard Ratio [95% CI]	0.38 [0.27, 0.54]		0.50 [0.39, 0.64]	
Log-rank Test p-value	<0.001		<0.001	
PFS at Updated Analysis 1 March 2015 (Studies 1 and 2)				
PFS Events n (%)	97 (42)	116 (51)	191 (62)	248 (81)
Median in months [95% CI]	68.6 [52.8, NE]	22.5 [18.8, 30.0]	46.3 [40.1, 56.6]	23.8 [21.0, 27.3]
Hazard Ratio [95% CI]	0.38 [0.28, 0.50]		0.53 [0.44, 0.64]	
OS at Updated Analysis 1 Feb 2016 (Studies 1 and 2)				
OS Events n (%)	82 (35)	114 (50)	143 (47)	160 (52)
Median in months [95% CI]	111 [101.8, NE]	84.2 [71.0, 102.7]	105.9 [88.8, NE]	88.1 [80.7, 108.4]
Hazard Ratio [95% CI]	0.59 [0.44, 0.78]		0.90 [0.72, 1.13]	

Date of Unblinding in Maintenance Study 1 and 2 = 17 December 2009 and 7 July 2010, respectively.
Auto-HSCT = autologous hematopoietic stem cell transplantation; CI = confidence interval; ITT = intent to treat; NE = not estimable; PFS = progression-free survival.
PFS at time of unblinding for Maintenance Study 2 was based on assessment by an Independent Review Committee. All other PFS analyses were based on assessment by investigator.
Note: The median is based on Kaplan-Meier estimate, with 95% CIs about the median overall PFS time. Hazard ratio is based on a proportional hazards model stratified by stratification factors comparing the hazard functions associated with treatment arms (REVLIMID:placebo).

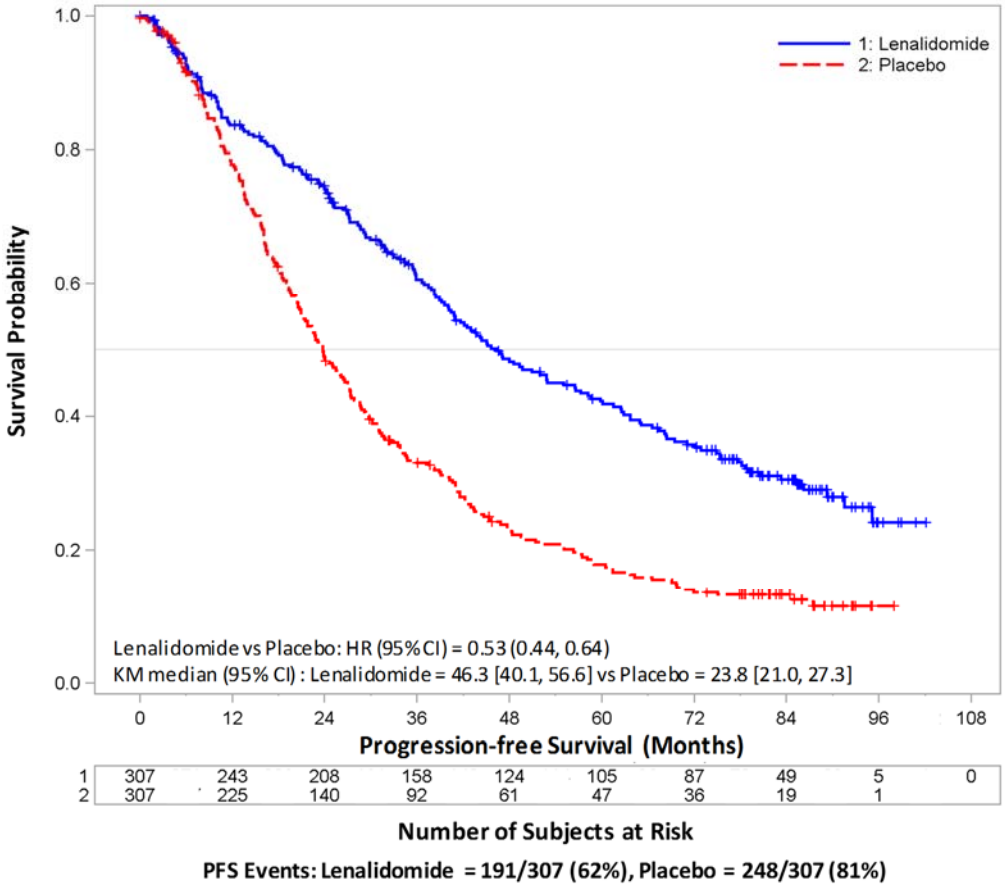
Kaplan-Meier Curves of Progression-free Survival from Randomization (ITT Post-Auto-HSCT Population) in MM Maintenance Study 1 between REVLIMID and Placebo Arms (Updated Cutoff Date 1 March 2015)



PFS Events: Lenalidomide = 97/231 (42%), Placebo = 116/229 (51%)

Auto-HSCT = autologous hematopoietic stem cell transplantation; CI = confidence interval; HR = hazard ratio; ITT = intent to treat; KM = Kaplan-Meier; PFS = progression-free survival; vs = versus.

Kaplan-Meier Curves of Progression-free Survival from Randomization (ITT Post-Auto-HSCT Population) in MM Maintenance Study 2 between REVLIMID and Placebo Arms (Updated Cutoff Date 1 March 2015)



PFS Events: Lenalidomide = 191/307 (62%), Placebo = 248/307 (81%)

Auto-HSCT = autologous hematopoietic stem cell transplantation; CI = confidence interval; HR = hazard ratio; ITT = intent to treat; KM = Kaplan-Meier; NE = not estimable; PFS = progression-free survival; vs = versus.

Randomized, Open-Label Clinical Studies in Patients with MM After At Least One Prior Therapy

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

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

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

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

Table 16 summarizes the baseline patient and disease characteristics in the two studies. In both studies, baseline demographic and disease-related characteristics were comparable between the REVLIMID/dexamethasone and placebo/dexamethasone groups.

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

	Study 1		Study 2	
	REVLIMID/Dex N=177	**Placebo/Dex N=176**	**REVLIMID/Dex N=176**	**Placebo/Dex N=175**
Patient Characteristics				
Age (years) Median Min, Max	 64 36, 86	 62 37, 85	 63 33, 84	 64 40, 82
Sex Male Female	 106 (60%) 71 (40%)	 104 (59%) 72 (41%)	 104 (59%) 72 (41%)	 103 (59%) 72 (41%)
Race/Ethnicity White Other	 141(80%) 36 (20%)	 148 (84%) 28 (16%)	 172 (98%) 4 (2%)	 175 (100%) 0 (0%)
ECOG Performance Status 0-1	 157 (89%)	 168 (95%)	 150 (85%)	 144 (82%)
Disease Characteristics				
Multiple Myeloma Stage (Durie-Salmon) I II III	 3% 32% 64%	 3% 31% 66%	 6% 28% 65%	 5% 33% 63%
β2-microglobulin (mg/L) ≤ 2.5 mg/L > 2.5 mg/L	 52 (29%) 125 (71%)	 51 (29%) 125 (71%)	 51 (29%) 125 (71%)	 48 (27%) 127 (73%)
Number of Prior Therapies				
1 ≥ 2	38% 62%	38% 62%	32% 68%	33% 67%
Types of Prior Therapies				
Stem Cell Transplantation	62%	61%	55%	54%
Thalidomide	42%	46%	30%	38%
Dexamethasone	81%	71%	66%	69%
Bortezomib	11%	11%	5%	4%
Melphalan	33%	31%	56%	52%
Doxorubicin	55%	51%	56%	57%

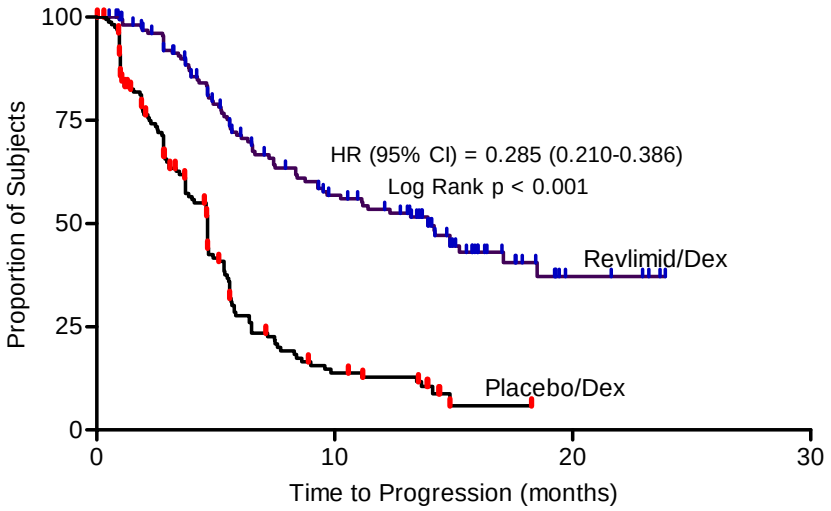
The primary efficacy endpoint in both studies was time to progression (TTP). TTP was defined as the time from randomization to the first occurrence of progressive disease.

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

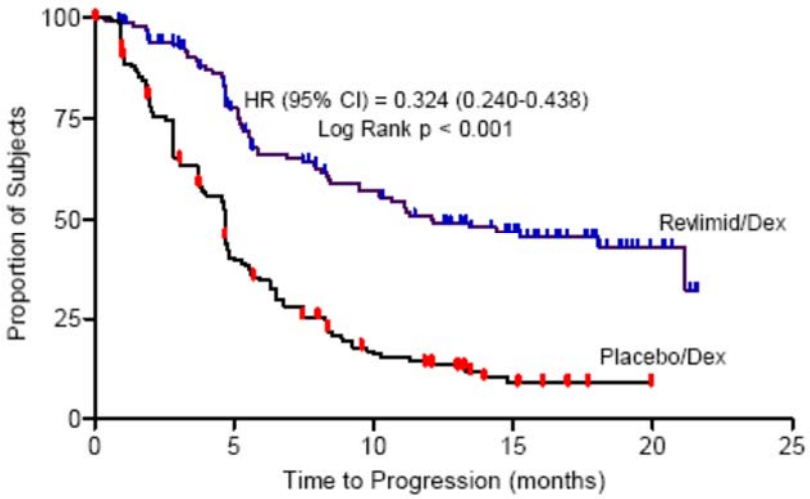
Table 17: TTP Results in MM Study 1 and Study 2

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

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



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



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

The efficacy and safety of 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 18.

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

	Overall (N=148)	
Age (years)		
Median	71	
Min, Max	37, 95	
Gender	**n**	**(%)**
Male	51	(34.5)
Female	97	(65.5)
Race	**n**	**(%)**
White	143	(96.6)
Other	5	(3.4)
Duration of MDS (years)		
Median	2.5	
Min, Max	0.1, 20.7	
Del 5 (q31-33) Cytogenetic Abnormality	**n**	**(%)**
Yes	148	(100)
Other cytogenetic abnormalities	37	(25.2)
IPSS Score [a]	**n**	**(%)**
Low (0)	55	(37.2)
Intermediate-1 (0.5-1.0)	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)
RARS	16	(10.8)
RAEB	30	(20.3)
CMML	3	(2)

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

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

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

RBC transfusion independence rates were unaffected by age or gender.

The dose of 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 REVLIMID was conducted to evaluate the safety and efficacy of REVLIMID 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 REVLIMID 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 REVLIMID 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 19: Baseline Disease-related Characteristics and Prior Anti –Lymphoma Therapy in Mantle Cell Lymphoma Trial

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

[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 20. The median time to response was 2.2 months (range 1.8 to 13 months).

Table 20: Response Outcomes in the Pivotal Mantle Cell Lymphoma Trial

Response Analyses (N = 133)		**N (%)**	**95% CI**
Overall Response Rate (IWRC) (CR + CRu +PR)		34 (26)	(18.4, 33.9)
Complete Response (CR + CRu)		9 (7)	(3.1, 12.5)
CR		1 (1)	
CRu		8 (6)	
Partial Response (PR)		25 (19)	
Duration of Response (months)		**Median**	**95% CI**
Duration of Overall Response (CR + CRu + PR)	(N = 34)	16.6	(7.7, 26.7)

14.4 Follicular and Marginal Zone Lymphoma

The efficacy of REVLIMID with rituximab in patients with relapsed or refractory follicular and marginal zone lymphoma was evaluated in the AUGMENT (NCT01938001) and MAGNIFY (NCT01996865) trials.

AUGMENT is a randomized, double-blind, multicenter trial (n=358) in which patients with relapsed or refractory follicular or marginal zone lymphoma were randomized 1:1 to receive REVLIMID and rituximab or rituximab and placebo. AUGMENT included patients diagnosed with Grade 1, 2, or 3a follicular lymphoma, who received at least 1 prior systemic therapy, were refractory or relapsed, not rituximab-refractory, had at least one measurable nodal or extranodal lesion by CT or MRI scan, and had adequate bone marrow, liver, and renal function. Randomization was stratified by follicular versus marginal zone lymphoma, previous rituximab therapy, and time since other anti-lymphoma therapy. In AUGMENT, REVLIMID was administered orally 20 mg once daily for Days 1 to 21 of repeating 28-day cycles for a maximum of 12 cycles or until unacceptable toxicity. The dose of rituximab was 375 mg/m^2 every week in Cycle 1 (Days 1, 8, 15, and 22) and on Day 1 of every 28-day cycle from Cycles 2 through 5. All dosage calculations for rituximab were based on the patient's body surface area (BSA), using actual patient weight. Dose adjustments for REVLIMID were allowed based on clinical and laboratory findings. A patient with moderate renal insufficiency (≥30 to <60 mL/minute) received a lower REVLIMID starting dose of 10 mg daily on the same schedule. After 2 cycles, the REVLIMID dose could be increased to 15 mg once daily on Days 1 to 21 of each 28-day cycle if the patient tolerated the medication.

MAGNIFY is an open-label, multicenter trial (n=232) in which patients with relapsed or refractory follicular, marginal zone, or mantle cell lymphoma received 12 induction cycles of REVLIMID and rituximab. MAGNIFY included patients diagnosed with Grade 1, 2,3a, 3b follicular (including transformed), marginal zone, or mantle cell lymphoma Stage I to IV who were previously treated for their lymphoma, had been refractory or had a relapse after their last treatment, had at least one measurable nodal or extranodal lesion by CT or MRI scan, and had adequate bone marrow, liver, and renal function. Patients refractory to rituximab were also included. The information from the subjects who received at least 1 dose of initial therapy in the first 12 induction cycles (n=222) in the MAGNIFY trial was included in the evaluation of the efficacy of REVLIMID/rituximab in patients with relapsed or refractory follicular and marginal zone lymphoma. In MAGNIFY, REVLIMID 20 mg was given on Days 1-21 of repeated 28-day cycles for up to 12 cycles or until unacceptable toxicity, progression, or withdrawal of consent. The dose of rituximab was 375 mg/m^2 every week in Cycle 1 (Days 1, 8, 15, and 22) and on Day 1 of every other 28-day cycle (Cycles 3,5,7,9, and 11) up to 12 cycles therapy. All dosage calculations for rituximab were based on the patient BSA and actual weight. Dose adjustments were allowed based on clinical and laboratory findings.

The demographic and disease-related baseline characteristics in the AUGMENT and MAGNIFY trials are shown in the following table.

Table 21: Baseline Demographics and Disease-Related Characteristics of Patients with FL and MZL in AUGMENT and MAGNIFY Trials

	AUGMENT Trial		**MAGNIFY Trial**
Parameter	**REVLIMID + Rituximab (N=178)**	**Rituximab + Placebo (Control Arm) (N=180)**	**REVLIMID + Rituximab (N=222)**
Age (years)			
Median (Max, Min)	64 (26, 86)	62 (35, 88)	65 (35, 91)
Age distribution, n (%)			
<65 years	96 (54)	107 (59)	103 (46)
≥65 years	82 (46)	73 (41)	119 (54)
Sex, n (%)			
Male	75 (42)	97 (54)	122 (55)
Female	103 (58)	83 (46)	100 (45)
Race			
White	118 (66)	115 (64)	206 (93)
Other races	54 (30)	64 (36)	14 (6)
Not collected or reported	6 (3)	1 (0.6)	2 (1)
Body Surface Area (BSA, m^2)			
Median (Max, Min)	1.8 (1.4, 3.1)	1.8 (1.3, 2.7)	2 (1.3, 2.6)
Disease Type FL or MZL			
Follicular lymphoma	147 (83)	148 (82)	177 (80)
Marginal zone lymphoma	31 (17)	32 (18)	45 (20)
MZL subtype at diagnosis (investigator), n (%)			
MALT	14 (45)	16 (50)	10 (22)
Nodal	8 (26)	10 (31)	25 (56)
Splenic	9 (29)	6 (19	10 (22)
FL stage at diagnosis (investigator), n (%)			
FL Grade 1-2	125 (85)	123 (83)	149 (84)
FL Grade 3a	22 (15)	25 (17)	28 (16)
FLIPI score at baseline (calculated), n (%)			Not Collected

Parameter	AUGMENT Trial		MAGNIFY Trial
	REVLIMID + Rituximab (N=178)	Rituximab + Placebo (Control Arm) (N=180)	REVLIMID + Rituximab (N=222)
Low risk (0,1)	52 (29)	67 (37)	
Intermediate risk (2)	55 (31)	58 (32)	
High risk (≥3)	69 (39)	54 (30)	
Missing	2 (1)	1 (0.6)	
ECOG score at baseline, n (%)			
0	116 (65)	128 (71)	102 (46)
1	60 (34)	50 (28)	113 (51)
2	2 (1)	2 (1)	7 (3)
High tumor burden[b] at baseline, n (%)			
Yes	97 (54)	86 (48)	148 (67)
No	81 (46)	94 (52)	74 (33)
Number of prior systemic antilymphoma therapies			
1	102 (57)	97 (54)	94 (42)
>1	76 (43)	83 (46)	128 (58)

Data Cutoff: 22 June 2018 (AUGMENT) and 1 May 2017 (MAGNIFY).
[a] Patient had either 0 (n=2) or 1 prior systemic therapy.
[b] Defined by GELF criteria.
ECOG = Eastern Cooperative Oncology Group; FLIPI = follicular lymphoma international prognostic index

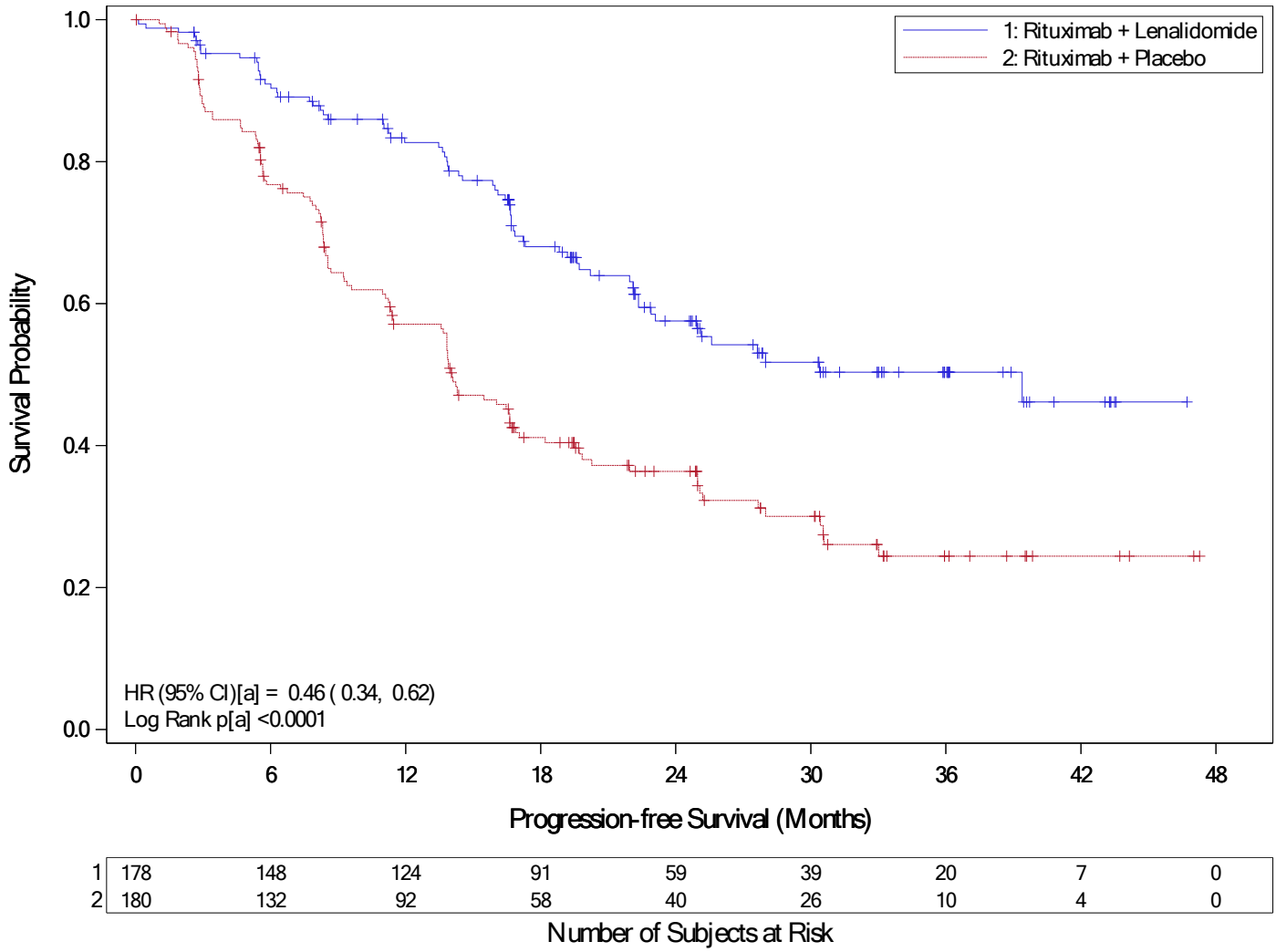
In AUGMENT, efficacy was established in the intent-to-treat (ITT) population based on progression-free survival by Independent Review Committee using modified 2007 International Working Group response criteria. Efficacy results are summarized in Table 22.

Table 22: Efficacy Results for Patients in the AUGMENT Trial (ITT FL and MZL Population)

Parameter	REVLIMID + Rituximab (N=178)	Rituximab + Placebo (N=180)
PFS		
Patients with event, n (%)	68 (38.2)	115 (63.9)
Death	6 (8.8)	2 (1.7)
Progression of disease	62 (91.2)	113 (98.3)
PFS, median [a] [95% CI] (months)	39.4 [22.9, NE]	14.1 [11.4, 16.7]
HR [b] [95% CI]	0.46 [0.34, 0.62]	
p-value [c]	<0.0001	
Objective response (CR+PR) , n(%) [95% CI] [d]	138 (77.5) [70.7, 83.4]	96 (53.3) [45.8, 60.8]

[a] Median estimate is from Kaplan-Meier analysis.
[b] hazard ratio and its CI were estimated from Cox proportional hazard model adjusting for the stratification 3: previous rituximab treatment (yes, no), time since last antilymphoma therapy (≤ 2, > 2 years), and disease histology (FL, MZL).
[c] p-value from log-rank test stratified by 3 factors noted above: previous rituximab treatment (yes, no), time since last antilymphoma therapy (≤ 2, > 2 years), and disease histology (FL, MZL).
[d] Exact confidence interval for binomial distribution.

Kaplan-Meier Curves of Progression-free Survival by IRC Assessment Between Arms in AUGMENT Trial (ITT FL and MZL Population)



a = Stratification factors included: previous rituximab treatment (y/n), time since last anti-lymphoma therapy (≤2 years, >2years), and disease histology (FL or MZL).
CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; PFS = progression-free survival

Follicular Lymphoma

In AUGMENT, the objective response by IRC assessment for patients with follicular lymphoma was 80% (118/147) [95% CI: 73%, 86%]) in REVLIMID with rituximab arm compared to 55% (82/148) [95% CI: 47, 64] in control arm.

In MAGNIFY, the overall response by investigator assessment was 59% (104/177) [95% CI: 51, 66] for patients with follicular lymphoma. Median duration of response was not reached with a median follow-up time of 7.9 months [95% CI: 4.6, 9.2].

Marginal Zone Lymphoma

In AUGMENT, the objective response by IRC assessment for patients with marginal zone lymphoma was 65% (20/31) [95% CI: 45%, 81%] in REVLIMID with rituximab arm compared to 44% (14/32) [95% CI: 26%, 62%] in control arm.

In MAGNIFY, the overall response by investigator assessment was 51% (23/45) [95% CI: 36, 66] for patients with marginal zone lymphoma. Median duration of response was not reached with a median follow-up time of 11.5 months [95% CI: 8.0, 18.9].

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)]*.

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
86 Morris Avenue
Summit, NJ 07901

Pat. www.celgene.com/therapies

RevPlyPI.026/MG.026

MEDICATION GUIDE

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

  Females who can become pregnant:
  - o Will have pregnancy tests weekly for 4 weeks, then every 4 weeks if your menstrual cycle is regular, or every 2 weeks if your menstrual cycle is irregular.
  - o If you miss your period or have unusual bleeding, you will need to have a pregnancy test and receive counseling.
  - o Must agree to use two acceptable forms of birth control at the same time, for at least 4 weeks before, while taking, during any breaks (interruptions) in your treatment, and for at least 4 weeks after stopping REVLIMID.
  - o Talk with your healthcare provider to find out about options for acceptable forms of birth control that you may use to prevent pregnancy before, during, and after treatment with REVLIMID.
  - o 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:
  - o FDA MedWatch at 1-800-FDA-1088, and
  - o 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:
  - o Males, including those who have had a vasectomy, must always use a latex or synthetic condom during any sexual contact with a pregnant female or a female 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.
  - o Do not have unprotected sexual contact with a female who is or could become pregnant. Tell your healthcare provider if you do have unprotected sexual contact with a female who is or could become pregnant.
  - o Do not donate sperm while taking 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 adults 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 2 prior medicines, one of which included bortezomib. MCL is a cancer of a type of white blood cell called lymphocytes that are in the lymph nodes.
- follicular lymphoma (FL) or marginal zone lymphoma (MZL)
  - in combination with a rituximab product, **and**
  - who have previously been treated for their FL or MZL

  FL and MZL are types of cancer of white blood cells called B-cell lymphocytes that are found in the lymph nodes and spleen.

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
- have had a serious skin rash with thalidomide treatment. You should not take REVLIMID.
- 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)
  - dark or brown (tea-colored) urine
  - pain on the upper right side of your stomach area (abdomen)
  - bleeding or bruising more easily than normal
  - feeling very tired
- **Severe skin reactions including severe allergic 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 severe allergic reaction or severe skin reaction during treatment with REVLIMID:
  - swelling of your face, eyes, lips, tongue, throat
  - trouble swallowing
  - trouble breathing
  - skin rash, hives, or peeling of your skin
  - blisters
  - rash with fever and or swollen glands
- **Tumor lysis syndrome (TLS).** TLS is caused by the fast breakdown of cancer cells. TLS can cause kidney failure and the need for dialysis treatment, abnormal heart rhythm, seizure and sometimes death. Your healthcare provider may do blood tests to check you for TLS.
- **Worsening of your tumor (tumor flare reaction).** Tell your healthcare provider if you get any of these symptoms of tumor flare reaction while taking 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.
- **Risk of Early Death in MCL.** In people who have Mantle Cell Lymphoma (MCL), there may be a risk of dying sooner (early death) when taking REVLIMID. Talk with your healthcare provider about any concerns and possible risk factors.

The most common side effects of REVLIMID include:

- diarrhea
- rash
- nausea
- constipation
- tiredness or weakness
- fever
- itching
- swelling of your arms, hands, legs, feet and skin
- sleep problems (insomnia)
- headache
- muscle cramps or spasms
- shortness of breath
- cough, sore throat, and other symptoms of a cold
- upper respiratory tract infection or bronchitis
- inflammation of the stomach and intestine (“stomach flu”)
- nose bleed
- shaking or trembling (tremor)
- joint aches
- pain in your back or stomach-area (abdomen)

These are not all the possible side effects of 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, 86 Morris Avenue, Summit, NJ 07901

For more information, call 1-888-423-5436 or go to www.CelgeneRiskManagement.com.

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

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