Table 2: Summary of Adverse Events Reported in ≥ 5% and Grade 3-4 Adverse Events in ≥ 1% of the Rd and Rd18 treated patients in the Transplant Non-Eligible Newly Diagnosed Multiple Myeloma Study

System organ class / Preferred term[a]	Rd (N=532)		Rd18 (N=540)		MPT (N=541)	
	All grades[b] n (%)	Grade[b] 3-4 n (%)	All grades[b] n (%)	Grade[b] 3-4 n (%)	All grades[b] n (%)	Grade[b] 3-4 n (%)
Investigations	**169 (31.8)**	**47 (8.8)**	**173 (32.0)**	**36 (6.7)**	**141 (26.1)**	**30 (5.5)**
Weight decreased	72 (13.5)	11 (2.1)	78 (14.4)	4 (0.7)	48 (8.9)	4 (0.7)
Blood creatinine increased	35 (6.6)	8 (1.5)	25 (4.6)	5 (0.9)	24 (4.4)	6 (1.1)
Cardiac Disorders	**155 (29.1)**	**63 (11.8)**	**106 (19.6)**	**39 (7.2)**	**129 (23.8)**	**46 (8.5)**
Atrial fibrillation	37 (7.0)	13 (2.4)	25 (4.6)	9 (1.7)	25 (4.6)	6 (1.1)
Cardiac failure	17 (3.2)	10 (1.9)	16 (3.0)	8 (1.5)	14 (2.6)	9 (1.7)
Cardiac failure congestive	14 (2.6)	8 (1.5)	7 (1.3)	6 (1.1)	9 (1.7)	6 (1.1)
Acute myocardial infarction	6 (1.1)	6 (1.1)	1 (0.2)	1 (0.2)	4 (0.7)	4 (0.7)
Renal & Urinary Disorders	**145 (27.3)**	**46 (8.6)**	**108 (20.0)**	**39 (7.2)**	**88 (16.3)**	**39 (7.2)**
Renal failure	28 (5.3)	12 (2.3)	33 (6.1)	18 (3.3)	22 (4.1)	16 (3.0)
Renal failure acute	23 (4.3)	18 (3.4)	22 (4.1)	16 (3.0)	15 (2.8)	13 (2.4)
Renal impairment	15 (2.8)	6 (1.1)	6 (1.1)	0 (0.0)	7 (1.3)	2 (0.4)
Ear & Labyrinth Disorders	**58 (10.9)**	**3 (0.6)**	**45 (8.3)**	**2 (0.4)**	**77 (14.2)**	**4 (0.7)**
Vertigo	27 (5.1)	2 (0.4)	20 (3.7)	1 (0.2)	35 (6.5)	1 (0.2)
Neoplasms Benign, Malignant & Unspecified (Including Cysts & Polyps)	**54 (10.2)**	**26 (4.9)**	**42 (7.8)**	**26 (4.8)**	**22 (4.1)**	**9 (1.7)**
Squamous cell carcinoma of skin	14 (2.6)	8 (1.5)	5 (0.9)	4 (0.7)	1 (0.2)	0 (0.0)

[a]System Organ Class and Preferred Terms are coded using the MedDRA dictionary version 15.1
[b]Severity Grades are based on US National Cancer Institute Common Toxicity Criteria version 3.0
d = low-dose dexamethasone; M = melphalan; P = prednisone; R = lenalidomide (REVLIMID®); T = thalidomide
When an adverse event was reported multiple times within a given preferred term, only one event with the worst severity was counted per subject. Data cutoff date = 24 May 2013.

In the study of patients with transplant non-eligible newly diagnosed multiple myeloma the following **serious adverse events (considered related to study drug treatment)** were reported in ≥ 1% of Rd and /or Rd18 treated patients:

Blood and Lymphatic System Disorders: anemia, neutropenia, febrile neutropenia
Cardiac Disorders: atrial fibrillation
General Disorders and Administration Site Conditions: general physical health deterioration
Infections and Infestations: pneumonia, sepsis
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps): squamous cell carcinoma of skin
Respiratory, Thoracic and Mediastinal Disorders: pulmonary embolism

Vascular Disorders: deep vein thrombosis

Phase 3 Randomized Double Blind Placebo-Controlled Studies in Previously Treated Multiple Myeloma Patients

Data were evaluated from 703 patients who received at least one dose of REVLIMID®/dexamethasone (353 patients) or placebo/dexamethasone (350 patients). Overall, the adverse event data demonstrate that the addition of REVLIMID® to dexamethasone was accomplished with only a minimal increase in toxicity. The incidences of lethargy, neutropenia, thrombocytopenia, anemia NOS, leukopenia NOS, lymphopenia, diarrhea NOS, constipation, dry mouth, rash NOS, dry skin, tremor, dizziness, dysgeusia, muscle cramp, back pain, dyspnea NOS, nasopharyngitis, pharyngitis, upper respiratory tract infection NOS, pneumonia NOS, anorexia, hypokalemia, hypocalcemia, hypomagnesemia, vision blurred, and DVT were higher in the REVLIMID®/dexamethasone group than in the placebo/dexamethasone group.

Based on pooled data from two studies, all subjects experienced at least one adverse event when on REVLIMID®/dexamethasone combination treatment. A greater proportion of patients in the REVLIMID®/dexamethasone group than in the placebo/dexamethasone group had grade 3/4 (83.3% vs. 69.7%) and serious (57.2% vs. 46.6%) adverse events. More patients taking REVLIMID®/dexamethasone had experienced an adverse event leading to dose reduction/interruption (76.5% vs. 57.7%) and drug discontinuation (24.9% vs. 18.0%). The incidences of serious cardiac and DVT events were 7.6% and 7.1% in the REVLIMID®/dexamethasone group as compared to 3.4% and 3.1% in the placebo/dexamethasone group, respectively (see **WARNINGS AND PRECAUTIONS**).

Treatment-emergent cardiac disorders of any kind were reported more frequently among subjects treated with REVLIMID®/dexamethasone (18.1%; 64/353) than in subjects treated with placebo/dexamethasone (11.1%, 39/350). A total of 33 serious cardiac events were reported in 27 REVLIMID®/dexamethasone subjects compared to 15 events in 12 placebo/dexamethasone subjects. Serious cardiac disorders included atrial fibrillation (12 vs. 2 subjects), cardiac failure congestive (5 vs. 0 subjects), acute myocardial infarction (3 vs. 0 subjects), coronary artery disease (3 vs. 0 subjects), atrial flutter (2 vs. 0 subjects), arteriospasm coronary (1 vs. 0 subjects), acute coronary syndrome (1 vs. 0 subjects), and pulmonary edema NOS (1 vs 4 subjects). For serious events of atrial fibrillation, the exposure adjusted incidence density was three-fold higher for the REVLIMID®/dexamethasone group than for the placebo/dexamethasone group (0.033 versus 0.010 events per person per year). If atrial fibrillation is detected, the patient should be treated in accordance with current medical practice in order to prevent potentially serious consequences.

Cardiac adverse events leading to the discontinuation of study medication were atrial fibrillation (2/353) and acute myocardial infarction (2/353) in the REVLIMID®/dexamethasone arm; and pulmonary edema NOS (3/350) in the placebo/dexamethasone arm.

Approximately 39% of subjects in the REVLIMID®/dexamethasone group required a reduction in their REVLIMID® dose, and approximately 31% of subjects required a reduction in their dexamethasone dose. Approximately 11% of subjects in the placebo/dexamethasone group required a reduction in their placebo dose and approximately 16% required a reduction in their dexamethasone dose.

Ten deaths were considered to be REVLIMID®/dexamethasone related: 3 due to cerebrovascular accident, 1 due to pneumonia, 1 due to leukoencephalopathy, 1 due to pulmonary embolism, 1 due to cardiac arrest, 1 due to pneumonia NOS/respiratory failure, 1 due to pancytopenia/pneumonia NOS/sepsis NOS and 1 due to sudden death of unknown causes.

Four deaths were considered placebo/dexamethasone related: 1 due to brain edema/pulmonary edema NOS, 1 due to pulmonary edema NOS, 1 due to pneumonia NOS, and 1 of unknown cause.

One case of hypersensitivity pneumonitis-like syndrome was reported with REVLIMID® use. The patient was dosed with REVLIMID® in cycles of 25 mg/d on days 1 to 21, followed by 7 days off. Dexamethasone was cycled at 40 mg/d on days 1–4, 9–12, and 17–20, followed by 7 days off. Treatment cycles were repeated every 28 days. In the case of unexpected respiratory symptoms such as dyspnea on exertion, crackles on physical examination, radiological bilateral ground-glass opacities and non-resolving pneumonia, REVLIMID® should be discontinued until further investigation excludes hypersensitivity pneumonitis-like syndrome.

Table 3 summarizes the number and percentage of subjects with Grade 1-4 adverse events reported in ≥5% of subjects in either treatment group.

Table 3: Summary of adverse events reported in ≥ 5% of the subjects in the Controlled Multiple Myeloma Studies

System organ class/ Preferred term	REVLIMID® /dexamethasone (N=353)	PLACEBO /dexamethasone (N=350)
Subjects With At Least One Adverse Event	353 (100.0)	350 (100.0)
General Disorders And Administration Site Conditions	**303 (85.8)**	**278 (79.4)**
Fatigue	161 (45.6)	147 (42.0)
Asthenia	103 (29.2)	94 (26.9)
Pyrexia	100 (28.3)	83 (23.7)
Edema Peripheral	95 (26.9)	75 (21.4)
Edema NOS	37 (10.5)	33 (9.4)
Chest Pain	30 (8.5)	21 (6.0)
Lethargy	26 (7.4)	8 (2.3)
Pain NOS	25 (7.1)	27 (7.7)
Gastrointestinal Disorders	**284 (80.5)**	**244 (69.7)**
Constipation	149 (42.2)	77 (22.0)
Diarrhea NOS	137 (38.8)	98 (28.0)
Nausea	92 (26.1)	76 (21.7)
Dyspepsia	59 (16.7)	51 (14.6)
Vomiting NOS	42 (11.9)	32 (9.1)
Abdominal Pain NOS	37 (10.5)	22 (6.3)
Abdominal Pain Upper	29 (8.2)	20 (5.7)
Dry Mouth	27 (7.6)	13 (3.7)
Stomatitis	22 (6.2)	19 (5.4)

Table 3: Summary of adverse events reported in ≥ 5% of the subjects in the Controlled Multiple Myeloma Studies

System organ class/ Preferred term	REVLIMID® /dexamethasone (N=353)	PLACEBO /dexamethasone (N=350)
Flatulence	20 (5.7)	16 (4.6)
Abdominal Distension	15 (4.2)	20 (5.7)
Musculoskeletal And Connective Tissue Disorders	**282 (79.9)**	**246 (70.3)**
Muscle Cramp	121 (34.3)	76 (21.7)
Back Pain	91 (25.8)	67 (19.1)
Arthralgia	63 (17.8)	63 (18.0)
Muscle Weakness NOS	56 (15.9)	56 (16.0)
Bone Pain	51 (14.4)	40 (11.4)
Pain In Limb	41 (11.6)	33 (9.4)
Myalgia	37 (10.5)	38 (10.9)
Chest Wall Pain	28 (7.9)	21 (6.0)
Nervous System Disorders	**275 (77.9)**	**221 (63.1)**
Headache	94 (26.6)	85 (24.3)
Dizziness	83 (23.5)	59 (16.9)
Tremor	75 (21.2)	26 (7.4)
Dysgeusia	54 (15.3)	34 (9.7)
Paraesthesia	51 (14.4)	47 (13.4)
Hypoaesthesia	37 (10.5)	26 (7.4)
Peripheral Neuropathy NOS	31 (8.8)	23 (6.6)
Neuropathy NOS	23 (6.5)	14 (4.0)
Respiratory, Thoracic And Mediastinal Disorders	**258 (73.1)**	**213 (60.9)**
Cough	90 (25.5)	86 (24.6)
Dyspnea NOS	85 (24.1)	60 (17.1)
Nasopharyngitis	65 (18.4)	31 (8.9)
Pharyngitis	53 (15.0)	34 (9.7)
Bronchitis NOS	41 (11.6)	30 (8.6)
Epistaxis	28 (7.9)	29 (8.3)
Hoarseness	22 (6.2)	17 (4.9)
Hiccups	21 (5.9)	17 (4.9)
Dyspnea Exertional	18 (5.1)	18 (5.1)
Infections And Infestations	**243 (68.8)**	**200 (57.1)**
Upper Respiratory Tract Infection NOS	87 (24.6)	55 (15.7)
Pneumonia NOS	49 (13.9)	30 (8.6)
Urinary Tract Infection NOS	31 (8.8)	19 (5.4)
Sinusitis NOS	30 (8.5)	17 (4.9)
Oral Candidiasis	22 (6.2)	19 (5.4)
Herpes Simplex	21 (5.9)	18 (5.1)
Respiratory Tract Infection NOS	18 (5.1)	11 (3.1)
Blood And Lymphatic System Disorders	**224 (63.5)**	**120 (34.3)**
Neutropenia	152 (43.1)	23 (6.6)
Anemia NOS	119 (33.7)	83 (23.7)
Thrombocytopenia	80 (22.7)	37 (10.6)
Leukopenia NOS	30 (8.5)	7 (2.0)
Lymphopenia	20 (5.7)	6 (1.7)
Psychiatric Disorders	**209 (59.2)**	**207 (59.1)**
Insomnia	129 (36.5)	133 (38.0)
Depression	45 (12.7)	37 (10.6)
Anxiety	35 (9.9)	33 (9.4)
Confusional State	33 (9.3)	24 (6.9)

Table 3: Summary of adverse events reported in ≥ 5% of the subjects in the Controlled Multiple Myeloma Studies

System organ class/ Preferred term	REVLIMID® /dexamethasone (N=353)	PLACEBO /dexamethasone (N=350)
Irritability	24 (6.8)	16 (4.6)
Mood Alteration NOS	10 (2.8)	28 (8.0)
Skin And Subcutaneous Tissue Disorders	**202 (57.2)**	**158 (45.1)**
Rash NOS	76 (21.5)	35 (10.0)
Sweating Increased	34 (9.6)	25 (7.1)
Dry Skin	33 (9.3)	16 (4.6)
Pruritus	26 (7.4)	18 (5.1)
Contusion	21 (5.9)	17 (4.9)
Night Sweats	18 (5.1)	17 (4.9)
Face Edema	15 (4.2)	20 (5.7)
Metabolism And Nutrition Disorders	**188 (53.3)**	**148 (42.3)**
Anorexia	57 (16.1)	36 (10.3)
Hyperglycemia NOS	57 (16.1)	50 (14.3)
Hypokalemia	52 (14.7)	21 (6.0)
Hypocalcaemia	34 (9.6)	10 (2.9)
Hypomagnesaemia	27 (7.6)	10 (2.9)
Appetite Decreased NOS	25 (7.1)	14 (4.0)
Dehydration	25 (7.1)	14 (4.0)
Investigations	**156 (44.2)**	**129 (36.9)**
Weight Decreased	68 (19.3)	53 (15.1)
Weight Increased	20 (5.7)	29 (8.3)
Vascular Disorders	**127 (36.0)**	**80 (22.9)**
Deep Vein Thrombosis	32 (9.1)	15 (4.3)
Hypertension NOS	30 (8.5)	22 (6.3)
Hypotension NOS	26 (7.4)	16 (4.6)
Eye Disorders	**121 (34.3)**	**91 (26.0)**
Vision Blurred	60 (17.0)	40 (11.4)
Endocrine Disorders	**32 (9.1)**	**22 (6.3)**
Cushingoid	21 (5.9)	16 (4.6)

System organ classes and preferred terms are coded using the MedDRA dictionary.
System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A subject with multiple occurrences of an AE is counted only once in the AE category.

Table 4 summarizes the Grade 3/4 adverse events reported in ≥2% of subjects in either treatment group.

Table 4: Incidence of grade 3/4 adverse events reported in ≥2% of subjects in Either Treatment Group

Preferred term**	REVLIMID®/ dexamethasone (N=353)	PLACEBO/ dexamethasone N=(350)
Subjects With At Least One Grade 3 / 4 AE	294	244
Neutropenia	125 (35.4)	12 (3.4)
Thrombocytopenia	46 (13.0)	22 (6.3)
Anemia NOS	38 (10.8)	21 (6.0)
Pneumonia NOS	32 (9.1)	19 (5.4)
Deep Vein Thrombosis	28 (7.9)	12 (3.4)
Hyperglycemia NOS	27 (7.6)	27 (7.7)
Fatigue	23 (6.5)	17 (4.9)
Hypokalemia	20 (5.7)	5 (1.4)
Muscle Weakness NOS	20 (5.7)	11 (3.1)
Asthenia	17 (4.8)	18 (5.1)
Hypocalcaemia	16 (4.5)	6 (1.7)
Atrial Fibrillation	14 (4.0)	4 (1.1)
Leukopenia NOS	14 (4.0)	1 (0.3)
Pulmonary Embolism	14 (2.0)	3 (0.9)
Diarrhea NOS	11 (3.1)	4 (1.1)
Lymphopenia	11 (3.1)	4 (1.1)
Depression	10 (2.8)	6 (1.7)
Dyspnea NOS	10 (2.8)	10 (2.9)
Hypophosphatemia	10 (2.8)	0 (0.0)
Syncope	10 (2.8)	4 (1.1)
Bone Pain	8 (2.3)	5 (1.4)
Confusional State	8 (2.3)	10 (2.9)
Constipation	8 (2.3)	2 (0.6)
Febrile Neutropenia	8 (2.3)	0 (0.0)
Dizziness	7 (2.0)	3 (0.9)
Nausea	7 (2.0)	2 (0.6)
Neuropathy NOS	7 (2.0)	4 (1.1)
Dehydration	6 (1.7)	8 (2.3)
Hypertension NOS	6 (1.7)	7 (2.0)
Pyrexia	5 (1.4)	12 (3.4)
Renal Failure NOS	5 (1.4)	11 (3.1)
Respiratory Tract Infection NOS	4 (1.1)	7 (2.0)
Hypotension NOS	3 (0.8)	7 (2.0)

*Adverse events with frequency ≥ 1% in the 10 mg. Grade 3 and 4 are based on National Cancer Institute Common Toxicity Criteria version 2.

**Preferred Terms are coded using the MedDRA dictionary. A patient with multiple occurrences of an AE is counted only once in the Preferred Term category.

In 2 pivotal studies of patients with multiple myeloma who had been treated with 1 prior therapy, the following **serious adverse events (considered related to study drug treatment)** were reported:

The frequency of undesirable effects was calculated using the CIOMS IV working group recommendation criteria:

Very common	≥1/10 (≥10%)
Common (frequent)	≥1/100 and <1/10 (≥1% and < 10%)
Uncommon (infrequent)	≥1/1000 and <1/100 (≥0.1% and < 1%)
Rare	≥1/10,000 and <1/1000 (≥0.01% and < 0.1%)
Very rare	< 1/10,000 (<0.01%)

Blood and Lymphatic system disorders:
Common: febrile neutropenia, neutropenia, anemia NOS, thrombocytopenia
Uncommon: pancytopenia, lymphadenopathy

Cardiac disorders:
Common: atrial fibrillation
Uncommon: cardiac failure congestive, atrial flutter

Endocrine disorders:
Uncommon: adrenal insufficiency NOS

Eye disorders:
Uncommon: blindness

Gastrointestinal disorders:
Uncommon: abdominal pain NOS, constipation, caecitis, diarrhea NOS, gastrointestinal hemorrhage NOS, peptic ulcer hemorrhage

General disorders and administration site conditions:
Common: pyrexia
Uncommon: general physical health deterioration, asthenia, edema peripheral

Infections and infestations:
Common: pneumonia NOS
Uncommon: cellulitis, sepsis NOS, bronchopneumonia NOS, herpes zoster ophthalmic, *Pneumocystis carnii* pneumonia, septic shock, urinary tract infection NOS, bursitis infective NOS, *Clostridium difficile* sepsis, *Enterobacter* bacteremia, *Escherichia* sepsis, herpes zoster, lobar pneumonia NOS, meningitis, neutropenic sepsis, pneumonia bacterial NOS, pneumonia pneumoccal, pneumonia primary atypical, respiratory tract infection NOS, sinusitis NOS, subacute endocarditis, upper respiratory tract infection NOS

Investigations:
Uncommon: international normalized ratio increased, blood creatinine increased, hemoglobin decreased, weight decreased, white blood cell count decreased

Metabolism and nutrition disorders:
Common: hyperglycemia NOS
Uncommon: dehydration, hypocalcaemia, hypokalemia

Musculoskeletal and connective tissue disorders:
Uncommon: muscle weakness NOS, myopathy steroid, back pain, spondylitis NOS

Neoplasms benign, malignant and unspecified (incl. cysts and polyps):
Uncommon: basal cell carcinoma, squamous cell carcinoma, glioblastoma multiforme, fibrous histiocytoma, breast carcinoma in situ, bronchoalveolar carcinoma, lung adenocarcinoma, prostate cancer, and transitional cell carcinoma*
* Each solid tumor listed as "Uncommon" above occurred in 1/353 patients.

Nervous system disorders:
Common: cerebrovascular accident
Uncommon: cerebral ischemia, dizziness, leukoencephalopathy, memory impairment, intracranial hemorrhage NOS, intracranial venous sinus thrombosis NOS, polyneuropathy NOS, somnolence

Psychiatric disorders:
Uncommon: depression, confusional state, delusion NOS, insomnia

Renal and urinary disorders:
Uncommon: renal failure NOS, renal failure acute, Fanconi syndrome acquired, hematuria, renal tubular necrosis, urinary retention

Respiratory, thoracic and mediastinal disorders:
Common: pulmonary embolism

Skin and subcutaneous tissue disorders:
Uncommon: skin discoloration

Vascular disorders:
Uncommon: venous thrombosis NOS limb, phlebitis NOS, hypotension NOS, peripheral ischemia, circulatory collapse, hypertension NOS, orthostatic hypotension, phlebitis superficial

Post-Market Adverse Drug Reactions

The following adverse drug reactions have been identified from the worldwide post-marketing experience with REVLIMID®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Allergic reactions: angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms

Endocrine Disorders: hyperthyroidism, hypothyroidism

Gastrointestinal Disorders: pancreatitis

General Disorders and Administrative Site Conditions: drug ineffective, drug intolerance, swelling, chills, edema, gait disturbance, feeling abnormal

Hepatobiliary Disorders: hepatic failure, acute hepatic failure, toxic hepatitis, cytolytic hepatitis, hepato-renal failure, cholestasis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis

Immune System Disorders: acute graft versus host disease

Infections and Infestations: Viral reactivation including herpes zoster virus and hepatitis B virus

Injury, Poisoning and Procedural Complications: hip fracture, fall

Investigations: RBC count decreased, platelet count decreased, WBC count decreased, blood pressure decreased, full blood count abnormal, hematocrit decreased, transient abnormal liver laboratory tests (predominantly transaminases). Treatment should be interrupted and restarted at a lower dose once levels return to baseline. Successful re-challenge without recurrence of liver laboratory elevation was reported in some patients.

Metabolism and Nutrition Disorders: tumor lysis syndrome (TLS) and tumor flare reaction (TFR)

Musculoskeletal Disorders: pain in extremity, rhabdomyolysis

Neoplasms benign, malignant and unspecified: multiple myeloma, leukemia, acute leukemia, acute myeloid leukemia, neoplasm progression, myelodysplastic syndromes

Nervous System Disorders: balance disorder, hypoesthesia

Renal Disorders: renal impairment

Reproductive System and Breast Disorders: breast mass, breast pain, erectile dysfunction

Respiratory, Thoracic and Mediastinal Disorders: dyspnea, interstitial pneumonitis, dysphonia, cough

Skin and Subcutaneous Tissue Disorders: pruritus, rash maculo-papular, skin exfoliation, erythema, swelling face, hyperhidrosis, urticaria, rash generalized

DRUG INTERACTIONS

Overview

In vitro lenalidomide is not a substrate, inhibitor or inducer of cytochrome P450 enzymes. Hence co-administration of cytochrome P450 substrates or inhibitors with REVLIMID® (lenalidomide) is not likely to result in clinically relevant drug-drug interactions.

Drug-Drug Interactions

Table 5: Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
digoxin	CT	When co-administered with REVLIMID®, the **digoxin** AUC was not significantly different, however, the **digoxin** C_{max} was increased by 14%.	Periodic monitoring of digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, is recommended during administration of REVLIMID®.
warfarin	CT	Co-administration of multiple doses of 10 mg of REVLIMID® had no effect on the single dose pharmacokinetics of R- and S- **warfarin**. Co-administration of single 25-mg dose of **warfarin** had no effect on the pharmacokinetics of total lenalidomide.	Expected changes in laboratory assessments of PT and INR were observed after warfarin administration, but these changes were not affected by concomitant REVLIMID® administration. Periodic monitoring of warfarin plasma levels, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, is recommended during administration of REVLIMID®.

Legend: CT = Clinical Trial; INR = International Normalized Ratio; PT = Prothrombin Time

The risk of DVT and PE may potentially be increased with the simultaneous use of erythropoietic agents or Hormone Replacement Therapy in menopause.

Hormonal contraceptives are not recommended due to the increased risk of venous thromboembolic disease.

Drug-Food Interactions

REVLIMID® is absorbed equally well with or without food.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

REVLIMID® may be associated with dizziness and fatigue. Therefore, patients are advised to be cautious when operating machinery, or when driving.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

Recommended Dose and Dosage Adjustment

- **Myelodysplastic Syndromes**

Recommended Starting Dose
The recommended starting dose of REVLIMID® for MDS patients is 10 mg daily for the first 21 days of repeated 28-day cycles. Dosing is continued or modified based upon clinical and laboratory findings.

Patients without at least a minor erythroid response within 4 months of therapy initiation demonstrated by at least a 50% reduction in transfusion requirements or, if not transfused, a 1 g/dL rise in hemoglobin, should discontinue REVLIMID® treatment.

Recommended Starting Dose Adjustment for Renal Impairment:
Since lenalidomide is primarily excreted unchanged by the kidney, starting dose adjustment is recommended in patients with renal insufficiency in order to maintain an effective and safe level of REVLIMID®. No dose adjustments are required for patients with CrCL ≥ 60 mL/min. A REVLIMID® starting dose adjustment should be considered for patients with CrCL < 60 mL/min.

The recommendations for initial starting doses of REVLIMID® for patients with MDS are as follows:

Renal Function (CrCL)	Myelodysplastic Syndromes Dose
Mild Renal Impairment (90 > CrCL ≥ 60 mL/min)	10 mg (Normal Dose) Every 24 hours
Moderate Renal Impairment (30 ≤ CrCL < 60 mL/min)	5 mg Every 24 hours
Severe Renal Impairment (CrCL < 30 mL/min, not requiring dialysis)	5 mg Every 48 hours
End Stage Renal Disease (CrCL < 30 mL/min, requiring dialysis)	5 mg 3 times a week following each dialysis

After initiation of REVLIMID® therapy, subsequent REVLIMID® dose modification should be based on individual patient treatment tolerance, as described below.

Recommended Dosage Adjustment

The dose of REVLIMID® was reduced or interrupted at least once due to an adverse event in 124 (83.8%) of the 148 patients; the median time to the first dose reduction or interruption was 22

days (mean, 48 days; range, 2-468 days), and the median duration of the first dose interruption was 22 days (mean, 31 days; range, 2-331 days). A second dose reduction or interruption due to adverse events was required in 73 (49.3%) of the 148 patients. The median interval between the first and second dose reduction or interruption was 71 days (mean, 117 days; range, 15-568 days) and the median duration of the second dose interruption was 23 days (mean, 35 days; range, 2-295 days). Among the 124 patients that had a dose reduction/interruption, the median dose per day was 4.3 mg (min=0.4, max=10.0) (see **CLINICAL TRIALS**).

Thrombocytopenia
MDS patients who are dosed initially at 10 mg and who experience thrombocytopenia should have their dosage adjusted as indicated in the following tables.

If thrombocytopenia develops WITHIN 4 weeks of starting treatment at 10 mg daily	
If baseline ≥100,000/mcL	
When Platelets	Recommended Course
Fall to <50,000/mcL	Interrupt REVLIMID® treatment
Return to ≥50,000/mcL	Resume REVLIMID® at 5 mg daily
If baseline <100,000/mcL	
When Platelets	Recommended Course
Fall to 50% of the baseline value	Interrupt REVLIMID® treatment
If baseline ≥60,000/mcL and returns to ≥50,000/mcL	Resume REVLIMID® at 5 mg daily
If baseline <60,000/mcL and returns to ≥30,000/mcL	Resume REVLIMID® at 5 mg daily

If thrombocytopenia develops AFTER 4 weeks of starting treatment at 10 mg daily	
When Platelets	Recommended Course
<30,000/mcL or <50,000/mcL with platelet transfusions	Interrupt REVLIMID® treatment
Return to ≥30,000/mcL (without hemostatic failure)	Resume REVLIMID® at 5 mg daily

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

If thrombocytopenia develops during treatment at 5 mg daily	
When Platelets	Recommended Course
<30,000/mcL or <50,000/mcL with platelet transfusions	Interrupt REVLIMID® treatment
Return to ≥30,000/mcL (without hemostatic failure)	Resume REVLIMID® at 5 mg every other day

Neutropenia
MDS patients who are dosed initially at 10 mg and experience neutropenia [Absolute Neutrophil Count (ANC)] should have their dosage adjusted as indicated in the following tables.

If neutropenia develops WITHIN 4 weeks of starting treatment at 10 mg daily	
If baseline ANC ≥1,000/mcL	
When Neutrophils	Recommended Course
Fall to <750/mcL	Interrupt REVLIMID® treatment
Return to ≥1,000/mcL	Resume REVLIMID® at 5 mg daily
If baseline ANC <1,000/mcL	
When Neutrophils	Recommended Course
Fall to <500/mcL	Interrupt REVLIMID® treatment
Return to ≥500/mcL	Resume REVLIMID® at 5 mg daily

If neutropenia develops AFTER 4 weeks of starting treatment at 10 mg daily	
When Neutrophils	Recommended Course
<500/mcL for ≥7 days or <500/mcL associated with fever (≥38.5°C)	Interrupt REVLIMID® treatment
Return to ≥500/mcL	Resume REVLIMID® at 5 mg daily

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

If neutropenia develops during treatment at 5 mg daily	
When Neutrophils	Recommended Course
<500/mcL for ≥7 days or <500/mcL associated with fever (≥38.5°C)	Interrupt REVLIMID® treatment
Return to ≥500/mcL	Resume REVLIMID® at 5 mg every other day

Other Grade 3/4 Toxicities
For other Grade 3/4 toxicities judged to be related to REVLIMID®, hold treatment and restart at a lower dose level when toxicity has resolved to ≤ Grade 2.

REVLIMID® interruption or discontinuation should be considered for Grade 2-3 skin rash. REVLIMID® must be discontinued for angioedema, skin rash Grade 4, exfoliative or bullous rash, or if SJS, TEN or DRESS is suspected, and should not be resumed following discontinuation from these reactions (see **WARNINGS AND PRECAUTIONS, Immune**).

- **Multiple Myeloma**

Recommended Starting Dose
The recommended starting dose of REVLIMID® for multiple myeloma patients is 25 mg/day administered as a single 25 mg capsule on Days 1-21 of repeated 28-day cycles in combination with dexamethasone.

In the treatment of transplant non-eligible newly diagnosed multiple myeloma (TNE NDMM) the recommended dose of dexamethasone is 40 mg orally once weekly (in patients > 75 years of age, the dexamethasone dose should be reduced to 20 mg once weekly) on days 1, 8, 15, and 22 of repeated 28-day cycles.

For previously treated multiple myeloma patients, refer to Clinical Trials for the dosing specifics of dexamethasone. Consideration should be given to the dose of dexamethasone used in combination with REVLIMID® in previously treated multiple myeloma patients (see **WARNINGS AND PRECAUTIONS**, **General**). In a Phase 3 clinical trial in newly diagnosed MM patients including both those that were transplant non-eligible and transplant eligible (newly diagnosed transplant-eligible is an unauthorized indication), patients randomized to the REVLIMID®/standard dose dexamethasone arm received REVLIMID® 25 mg/day, Days 1-21 every 28 days plus dexamethasone 40 mg/day on Days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg/day orally on Days 1-4 every 28 days. Patients randomized to the REVLIMID®/low dose dexamethasone arm received REVLIMID® 25 mg/day, Days 1-21 every 28 days plus low dose dexamethasone 40 mg/day once weekly on Days 1, 8, 15, and 22 every 28 days.

Dosing of REVLIMID® in combination with dexamethasone is continued or modified based upon clinical and laboratory findings until disease progression or intolerance.

Patients on therapy for Multiple Myeloma should have their complete blood counts monitored every 7 days (weekly) for the first 2 cycles (8 weeks), on days 1 and 15 of cycle 3, and every 28 days (4 weeks) thereafter. Patients may require dose interruption and/or reduction.

Recommended Starting Dose Adjustment for Renal Impairment:
Since lenalidomide is primarily excreted unchanged by the kidney, starting dose adjustment is recommended in patients with renal insufficiency in order to maintain an effective and safe level of REVLIMID®. No dose adjustments are required for patients with CrCL ≥ 60 mL/min. A REVLIMID® starting dose adjustment should be considered for patients with CrCL < 60 mL/min.

The recommendations for initial starting doses of REVLIMID® for patients with MM are as follows while maintaining a 21 out of 28 day treatment cycle:

Renal Function (CrCL)	Multiple Myeloma Dose
Mild Renal Impairment (90 > CrCL ≥ 60 mL/min)	25 mg (Normal Dose) Every 24 hours
Moderate Renal Impairment (30 ≤ CrCL < 60 mL/min)	10 mg[a] Every 24 hours
Severe Renal Impairment (CrCL < 30 mL/min, not requiring dialysis)	15 mg Every 48 hours
End Stage Renal Disease (CrCL < 30 mL/min, requiring dialysis)	5 mg Once daily. On dialysis days the dose should be administered following dialysis

[a]The dose may be escalated to 15 mg every 24 hours after 2 cycles if patient is not responding to treatment and is tolerating the drug.

After initiation of REVLIMID® therapy, subsequent REVLIMID® dose modification should be based on individual patient treatment tolerance, as described below.

Recommended Dosage Adjustment

Dose modification guidelines, as summarized below are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicity judged to be related to REVLIMID®.

Platelet counts
Thrombocytopenia

Newly Diagnosed Multiple Myeloma	
When Platelets	***Recommended Course***
Fall to < 25,000/mcL	Interrupt REVLIMID® treatment, follow CBC weekly
Return to ≥ 50,000/mcL	Restart REVLIMID® at 5 mg less than the previous dose. If previous dose was 5 mg, restart REVLIMID® at 2.5 mg. Do not dose below 2.5 mg daily.
Previously Treated Multiple Myeloma	
When Platelets	***Recommended Course***
Fall to <30,000/mcL	Interrupt REVLIMID® treatment, follow CBC weekly
Return to ≥30,000/mcL	Restart REVLIMID® at 15 mg daily (if starting dose was 25 mg daily), or 5 mg less than the adjusted starting dose.
For each subsequent drop <30,000/mcL	Interrupt REVLIMID® treatment
Return to ≥30,000/mcL	Resume REVLIMID® at 5 mg less than the previous dose. Do not dose below 5 mg daily

Neutrophil counts (ANC)
Neutropenia

Newly Diagnosed Multiple Myeloma	
When ANC	***Recommended Course***
Fall to < 500/mcL or febrile neutropenia (ANC < 1000/mcL & fever ≥ 38.5˚C)	Interrupt REVLIMID® treatment, add G-CSF, follow CBC weekly
Return to ≥ 1,000/mcL and neutropenia is the only toxicity	Resume REVLIMID® at starting dose
Return to ≥ 1,000/mcL and if other toxicity	Restart REVLIMID® at 5 mg less than the previous dose. If previous dose was 5 mg, restart REVLIMID® at 2.5 mg. Do not dose below 2.5 mg daily.
For each subsequent drop < 500/mcL or febrile neutropenia (ANC <1000 /mcL &fever ≥ 38.5˚C)	Interrupt REVLIMID® treatment
Return to ≥1,000/mcL	Resume REVLIMID® at 5 mg less than the previous dose. If previous dose was 5 mg, restart REVLIMID® at 2.5 mg. Do not dose below 2.5 mg daily.
Previously Treated Multiple Myeloma	
When ANC	***Recommended Course***
Fall to <1000/mcL	Interrupt REVLIMID® treatment, add G-CSF, follow CBC weekly
Return to ≥1,000/mcL and neutropenia is the only toxicity	Resume REVLIMID® at 25 mg daily (or adjusted starting dose).
Return to ≥1,000/mcL and if other toxicity	Resume REVLIMID® at 15 mg daily (if starting dose was 25 mg daily), or 5 mg less than the adjusted starting dose.
For each subsequent drop <1,000/mcL	Interrupt REVLIMID® treatment
Return to ≥1,000/mcL	Resume REVLIMID® at 5 mg less than the previous dose. Do not dose below 5 mg daily

ANC = Absolute neutrophil count; CBC = complete blood count; GCSF= granulocyte colony stimulating factor

Other Grade 3/4 Toxicities
For other Grade 3/4 toxicities judged to be related to REVLIMID®, hold treatment and restart at a lower dose level when toxicity has resolved to ≤ Grade 2.

REVLIMID® interruption or discontinuation should be considered for Grade 2-3 skin rash. REVLIMID® must be discontinued for angioedema, skin rash Grade 4, exfoliative or bullous rash, or if Stevens-Johnson syndrome, toxic epidermal necrolysis or drug reaction with eosinophilia and systemic symptoms is suspected, and should not be resumed following discontinuation from these reactions (see **WARNINGS AND PRECAUTIONS, Immune**).

Missed Dose

If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day. Patients should not take 2 doses at the same time.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Information on overdosage of REVLIMID® is limited. No cases of overdose have been reported during the clinical studies. The highest single dose of lenalidomide that has been ingested in humans in healthy volunteers is 400 mg and the highest multiple dose is 200 mg/day, administered as 100 mg twice daily for six days. There is no known specific antidote for REVLIMID® overdosage and treatment must be symptomatic. In the event of an overdosage, frequent monitoring of the patient's vital signs and blood counts over the following 2 weeks along with close patient monitoring are indicated. Appropriate supportive care should be administered.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of lenalidomide remains to be fully characterized; however, multiple mechanisms of action have been identified that affect cancer cells and their microenvironment.

Lenalidomide increases hemoglobin expression by erythroid cells; inhibits proliferation of certain hematopoietic tumor cells (including tumor cells with or without deletions of chromosome 5 and MM tumor cells); enhances T cell and Natural Killer cell number and activity; inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels; and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes.

Pharmacodynamics

In healthy volunteers, multiple dosing with lenalidomide appeared to have an effect upon the immune response. The highest dose was 200 mg/day. Dosing occurred once on the morning of Days 1 and 8 and twice daily on Days 2 to 7 inclusive. Statistically significant dose-related decrease in both CD4 and CD8 blood counts was observed from Day 4 onwards. For CD4 counts, the magnitude of the decreases was relatively constant (approximately 300/mm^3) on Days 4, 6 and 8, with values approaching 433/mm^3. The decrease in mean CD8 counts were up to 242/mm^3on Day 8, with levels still considerably lower than the baseline value at the post-study assessment.

Electrocardiography

A double-blind, randomised, placebo- and active-controlled, single-dose, four-period crossover study was performed to investigate the effects of lenalidomide 10 mg and 50 mg on ECG parameters in healthy male subjects (N=52). Lenalidomide at 10 mg and 50 mg single doses was not observed to affect the QTcF interval, the QRS duration, the PR interval, or heart rate in a treatment related manner.

- **Myelodysplastic Syndromes**

Treatment with lenalidomide in MDS patients is associated with apoptosis of dysplastic cells in the bone marrow of these patients. Whether long-term REVLIMID® therapy affects the CD4 and CD8 counts in MDS patients is not yet known.

- **Multiple Myeloma**

Treatment with lenalidomide in MM patients is associated with the induction of antiproliferative effects and apoptosis in malignant myeloma cells due to direct antitumor activity, the alteration of the bone marrow microenvironment, and immune modulation.

Pharmacokinetics

The pharmacokinetics of lenalidomide were evaluated in a single-blind, placebo-controlled, ascending single oral-dose study (see Table 6). Single oral doses of 5, 20, 50, 100, 200 and 400 mg were administered in the fasted state. Nineteen subjects entered the study and 15 completed the study.

Table 6: Summary of Pharmacokinetic Parameters in a healthy male volunteers Geometric Mean

Dose	C_{max} (ng/mL)	$t_{½}$ (h)	$AUC_{(0-\infty)}$ (ng·h/mL)	Apparent Oral Clearance (mL/min)	Apparent Volume of distribution (L)
5 mg	66.2	3.24	276	302	84.6
20 mg	373	3.66	1391	240	76.0
50 mg	808	3.46	2546	327	98.1
100 mg	1735	4.71	5997	278	113
200 mg	3519	5.16	12111	275	123
400 mg	4586	8.72	21895	304	230

No formal bioavailability studies were performed in humans.

The pharmacokinetics of lenalidomide were evaluated in MDS subjects who received a single 10 mg dose of REVLIMID® or multiple doses of REVLIMID® (see Table 7).

Table 7: Pharmacokinetic Parameters for Lenalidomide in MDS Subjects

Parameter	Single 10 mg Dose (N = 12)	Multiple Doses (N = 24)
C_{max} (ng/mL)	179 (33.6)	185 (38.7)
AUC_5 (ng•h/mL)	543 (27.5)	563 (32.5)
$t_{1/2,z}$ (h)	3.72 (19.5)	NA

Geometric mean (CV%) data are presented for all parameters; AUC = area under the concentration versus time curve from time zero to 5 hours; C_{max} = maximum concentration; $t_{1/2,z}$ = terminal half-life

Absorption:

Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration (C_{max}) by 36%. The pharmacokinetic disposition of lenalidomide is linear. C_{max} and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.
In patients with low- or intermediate-1-risk MDS, a single 10 mg oral dose of lenalidomide is rapidly absorbed with the C_{max} observed at around 1 hour post-dose. There is no accumulation of lenalidomide in plasma with multiple doses at 10 mg per day. The mean exposure (AUC_∞) in MDS patients is approximately 57% higher than healthy male subjects, possibly related to reduced renal function associated with the MDS disease state and secondary to increased age in this patient population. In two subjects with $30 \leq CrCL < 50$ mL/min, the 5-hour exposure (AUC) on Day 14 was increased by more than 70%, compared with the subjects with CrCL > 80 mL/min.

In MM patients maximum plasma concentrations occurred between 0.5 and 4.0 hours post-dose both on Days 1 and 28. AUC and C_{max} values increase proportionally with dose following single and multiple doses. Exposure (AUC) in multiple myeloma patients was 57% higher than in healthy male volunteers.

Distribution:

In vitro (^{14}C)-lenalidomide binding to plasma proteins is approximately 23-29%.

Lenalidomide is present in semen (<0.01% of the dose) after the administration of 25 mg/day. Lenalidomide is undetectable in the semen of healthy volunteers three days after discontinuation of the drug.

Metabolism:

Lenalidomide is not a substrate of hepatic metabolic enzymes in vitro. Unchanged lenalidomide is the predominant circulating component in vivo in humans. Two identified metabolites are hydroxy-lenalidomide and N-acetyl-lenalidomide; each constitutes less than 5% of parent levels in circulation.

In vitro in human liver preparations lenalidomide does not undergo oxidative (cytochrome P450) or conjugative metabolism. Non-enzymatic hydrolysis of lenalidomide occurs in aqueous media and plasma. In vitro lenalidomide does not inhibit or induce cytochrome P450 enzymes, suggesting that clinically relevant drug-drug interactions with cytochrome P450 substrates are unlikely.

Excretion:

In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore active secretion may have some contribution in the overall renal excretion of lenalidomide. Lenalidomide is a weak substrate, but not an inhibitor of P-glycoprotein, suggesting that drug-drug interactions are unlikely with P-glycoprotein substrates and inhibitors.

In MDS patients, urinary excretion of unchanged lenalidomide in 24 hours post-dose averages approximately 65% of the administered dose.
At recommended doses (5 to 25 mg/day), half-life in plasma is approximately 3 hours in healthy volunteers and ranged from 3 to 5 hours in patients with multiple myeloma or MDS.

Special Populations and Conditions

Pediatrics: No pharmacokinetic (PK) data are available in patients below the age of 18 years.

Geriatrics: No dedicated clinical studies have been conducted to evaluate pharmacokinetics of lenalidomide in the elderly. Population PK analyses included patients with ages ranging from 39 to 85 years old, of which 40.8 % were older than 65 years of age, and show that age does not influence the disposition of lenalidomide.

Gender: Based on a population PK analysis of pooled PK dataset containing 147 patients (M/F, 102/45) gender has no effect on lenalidomide pharmacokinetics.

Race: Based on PK studies in Asian patients, there are no clinically relevant differences in the lenalidomide PK parameters when compared to PK parameters obtained in Caucasian patients [see **DETAILED PHARMACOLOGY**].

Hepatic Insufficiency: Population PK analyses included patients with mild hepatic impairment (N = 16, total bilirubin >1.0 to ≤ 1.5 x ULN or AST > ULN) and show that mild hepatic impairment does not influence the disposition of lenalidomide. There are no data available for patients with moderate to severe hepatic impairment.

Renal Insufficiency: The pharmacokinetics of lenalidomide were studied in patients with renal impairment due to nonmalignant conditions. In this study, 5 patients with mild renal function impairment (CrCL 56-74 mL/min), 6 patients with moderate renal function impairment (CrCL 33-46 mL/min), 6 patients with severe renal function impairment (CrCL 17-29 mL/min), and 6 patients with end stage renal disease requiring dialysis were administered a single oral 25 mg dose of REVLIMID®. As a control group comparator, 7 healthy subjects of similar age with normal renal function (CrCL 83-145 mL/min) were also administered a single oral 25 mg dose of REVLIMID®. The pharmacokinetic parameters of lenalidomide were similar in patients with mild impairment and healthy subjects. Patients with moderate and severe renal impairment had a 3-fold increase in half-life and up to 75% decrease in clearance compared to healthy subjects. Patients with end stage renal disease on hemodialysis had an approximately 4.5-fold increase in half-life and an 80% decrease in clearance compared to healthy subjects. Approximately 30% of the drug in the body was removed by a 4-hour dialysis session.

Mean AUC_{∞} was increased by 137%, 274% and 372% in patients with moderate, severe and end stage renal disease, respectively, as compared to that of normal and mild groups combined (n=12). Renal impairment had no effect on oral absorption (C_{max} and t_{max}).

After a single 10 mg dose of REVLIMID® in MDS patients with mild renal impairment, the drug exposure (AUC_{∞}) was increased by 55% and the apparent total clearance was reduced by 35% compared to those observed in MDS patients with normal renal function. In two MDS patients with moderate renal impairment, lenalidomide exposure after multiple doses was increased to a greater degree (C_{max} increased by 41-51% and AUC_{5} by 74-95%) while renal clearance was decreased by 65-92%. A starting dose adjustment is recommended for MDS patients with moderate renal impairment **(see DOSAGE AND ADMINISTRATION, Starting Dose Adjustment for Renal Impairment, Myelodysplastic Syndromes)**.

STORAGE AND STABILITY

Store at 15-30ºC.

SPECIAL HANDLING INSTRUCTIONS

Currently, no published data are available regarding the cutaneous absorption of lenalidomide. Most health care institutions recommend that latex gloves be worn while handling chemotherapeutic agents. Health care providers may consider wearing gloves when directly handling REVLIMID® (lenalidomide) capsules, along with standard hand washing. Females who could become pregnant, or who plan to become pregnant can handle REVLIMID® capsules if they are using latex gloves.

Patients should be instructed to not extensively handle or open the capsules and to maintain storage of capsules in blister packs until ingestion wherever possible. If there is contact with non-intact REVLIMID® capsules or the powder contents, the exposed area should be washed with soap and water.

Repackaging of REVLIMID® must only be done on exceptional circumstances. This should only be done by pharmacists.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each capsule contains the active ingredient, lenalidomide.

Each capsule contains the nonmedicinal ingredients: croscarmellose sodium, lactose anhydrous, magnesium stearate, and microcrystalline cellulose. The additional composition of the different capsule strengths is provided in the table below.

2.5 mg	REV, 2.5 mg	FD&C blue #2, gelatin, titanium dioxide, yellow iron oxide	White opaque and blue/green opaque	21 count blisters
5 mg	REV, 5 mg	Gelatin, titanium dioxide	White opaque	28 count blisters
10 mg	REV, 10 mg	FD&C blue #2, gelatin, titanium dioxide, yellow iron oxide	Blue/green opaque and pale yellow opaque	28 count blisters
15 mg	REV, 15 mg	FD&C blue #2, gelatin, titanium dioxide	Powder blue opaque and white opaque	21count blisters
20 mg	REV, 20 mg	FD&C blue #2, gelatin, titanium dioxide, yellow iron oxide	Blue-green opaque and powder blue opaque	21 count blisters
25 mg	REV, 25 mg	Gelatin, titanium dioxide	White opaque	21count blisters

*Imprint is in black ink

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

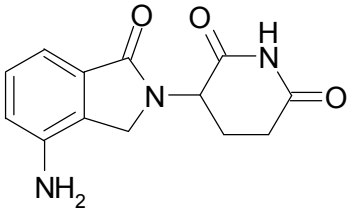
Drug Substance

Common name: lenalidomide

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

Molecular formula and molecular mass: $C_{13}H_{13}N_3O_3$, 259.3

Structural formula:



Physicochemical properties: 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. 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.

CLINICAL TRIALS

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

Two studies were conducted in support of the efficacy and safety of REVLIMID® (lenalidomide) in the treatment of transfusion dependent anemia due to Low- or Intermediate-1- risk MDS with a 5q (q31-33) cytogenetic abnormality in isolation or with additional cytogenetic abnormalities

Study demographics and trial design

The first study was a Phase 2, multicenter, open-label, single-arm study that was conducted to confirm the efficacy and safety of REVLIMID® in subjects with an International Prognostic Scoring System (IPSS) diagnosis of Low- or Intermediate-1-risk MDS associated with a 5q (q31-33) cytogenetic abnormality (del 5q) in isolation or with additional cytogenetic abnormalities, and RBC transfusion dependent anemia. REVLIMID® was dosed orally as 10 mg once daily continuously or 10 mg once daily for 21 days every 28 days. The study was not designed nor powered to prospectively compare the efficacy of the two dosing regimens. Sequential dose reductions to 5 mg daily and 5 mg every other day, as well as dose delays, were allowed for toxicity. This 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

$\geq 50{,}000/mm^3$, serum creatinine ≤ 2.5 mg/dL, serum SGOT/AST or SGPT/ALT ≤ 3.0 x upper limit of normal (ULN), and serum direct bilirubin ≤ 2.0 mg/dL.

The second study was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study comparing 2 doses of oral REVLIMID® versus placebo in RBC transfusion-dependent subjects with Low- or Intermediate-1-risk IPSS MDS associated with a del 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. This study was conducted in 2 phases: a double-blind treatment phase (up to maximum of 52 weeks) in which 205 subjects were randomized to receive either 10 mg REVLIMID® for 21 days of a 28-day cycle (cyclic), 5 mg REVLIMID® continuously, or placebo; and an open-label extension phase (maximum of 105 weeks). Subjects who successfully completed the double blind phase and subjects who did not have at least a minor erythroid response (50% reduction in RBC transfusions) by week 16 of double blind treatment were unblinded and eligible to receive open label REVLIMID® in either the 5 mg or 10 mg dosing regimens.

Baseline patient and disease-related characteristics for subjects in the IIT populations of the two studies are summarized below.

Table 8: Baseline Demographic and Disease-Related Characteristics

Parameter	Phase 2 Study (N=148)	Phase 3 Study (n = 205)
Age (years)		
Mean	70.0	67.3
SD	10.5	10.66
Median	71.0	68.0
Min, Max	37.0, 95.0	36.0, 86.0
Age distribution	**n (%)**	**n (%)**
< 65	48 (32.4)	82 (40.0)
> 65	100 (67.6)	123 (60.0)
Gender	**n (%)**	**n (%)**
Male	51 (34.5)	49 (23.9)
Female	97 (65.5)	156 (76.1)
Race	**n (%)**	**n (%)**
White	143 (96.6)	202 (98.5)
Other	5 (3.4)	3 (1.5)
Duration of MDS (years)		
Mean	3.4	3.6
SD	3.29	3.57
Median	2.5	2.6
Min, Max	0.1, 20.7	0.2, 29.2
Del 5 (q31-33) Cytogenetic Abnormality	**n (%)**	**n (%)**
Yes	148 (100.0)	191 (93.2)
Other cytogenetic abnormalities	37 (25.2)	-
IPSS Score [a] from central review	**n (%)**	**n (%)**
Low (0)	49 (33.1)	70 (34.1)
Intermediate-1 (0.5-1.0)	69 (46.6)	74 (36.1)
Intermediate-2 (1.5-2.0)	7 (4.7)	10 (4.9)
High (>=2.5)	2 (1.4)	1 (0.5)
Missing	21 (14.2)	50 (24.4)
FAB Classification [b] from central review	**n (%)**	**n (%)**
RA	78 (52.7)	107 (52.2)
RARS	16 (10.8)	24 (11.7)
RAEB	30 (20.3)	22 (10.7)
CMML	3 (2.0)	3 (1.5)

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

Study results

The International Working Group (IWG) defined criteria for a major erythroid response is transfusion independence for at least 8 consecutive weeks (56 days). In the Phase 2 study, transfusion independence was defined as a period of at least 56 consecutive days during which no transfusions were given and the Hgb concentration rose by at least 1 g/dL. In the Phase 3 study, the primary efficacy endpoint extended the transfusion independence period to 6 months (182 days).

An overview of the efficacy results for the Intent to Treat (ITT) populations is presented in Table 9 below. The primary endpoint results for the phase 3 study are provided (transfusion independence at 182 days), but for comparison purposes across studies the results by IWG criteria are shown. Results for the 5mg group are not displayed.

RBC-transfusion independence rates were unaffected by age or gender.

Table 9: Efficacy results for REVLIMID® in del 5q MDS (ITT populations)

Efficacy parameter	Phase 2 study	Phase 3 study (double-blind and open-label phases)	
	REVLIMID® 10 mg N = 148	REVLIMID® 10 mg N=69	Placebo N=67
Transfusion independence Number (%) transfusion independent (56 days) [a]	97 (65.5)	42 (60.9)	5 (7.5)
Number (%) transfusion independent (182 days) ^	86 (58.1)	37 (53.6)	4 (6.0)
Median Hgb increase (g/dL)[b] (Min, Max)	5.6 (2.2, 40.7)	6.2 (1.8, 10.0)	2.6 (1.5, 4.4)
Median Time to transfusion independence (weeks)[c] (Min, Max)	4.1 (0.3, 49.0)	4.6 (0.3, 14.7)	0.3 (0.3, 24.1)

CI = Confidence interval; Cont = continuous (28 days of a 28-day cycle); Cyc = cyclic (21 days of a 28-day cycle); Hgb = Hemoglobin; ITT = Intent to treat; Max = Maximum; Min = Minimum; MITT = Modified intent to treat; RBC = Red blood cell; SD = Standard deviation; nr = not reported.

* Based on RBC-transfusion independence response for subjects in the double-blind phase who became RBC-transfusion independent for at least 56 days

^ RBC-transfusion independence response for subjects in the double-blind phase who became RBC-transfusion independent for at least 182 days (MDS-004 primary endpoint)

a The absence of the intravenous infusion of any RBC transfusion during any consecutive "rolling" 56 days during the treatment period and an increase in Hgb of at least 1 g/dL from the minimum during the screening/baseline period to the maximum during the transfusion-independent period, excluding the first 30 days after the last transfusion before the transfusion-free period.

b Change from baseline in Hgb concentration to maximum value during response period, where response period was defined as the time from 30 days after the last transfusion prior to achieving transfusion independence to the next transfusion or to the last assessment for subjects who did not receive a subsequent transfusion during the study period.

c Measured from the day of the first dose of study drug to the first day of the first 56-day RBC transfusion-free period.

Multivariate analysis reveals that, compared to baseline, either a decrease in the ANC by 75 percent (in patients not neutropenic at baseline) or a decrease in the platelet count by 50 percent (regardless of the platelet count at baseline) within the first 8 weeks of the initiation of REVLIMID® is a predictor of red blood cell transfusion independence response.

Red blood cell transfusion independence correlated with decrease in platelet and/or neutrophil count (p=0.018 and p=0.005, respectively). The median decrease from baseline in absolute neutrophil counts was 1.73 x 10^9/L (Min, Max: 1.28 x 10^9/L, 20.35 x 10^9/L). The median decrease in platelet levels from maximum at baseline to the minimum during the study was 171 x 10^9/L (Min, Max: 32 x 10^9/L, 1393 x 10^9/L). Cytopenias were seen early in treatment (before onset of response) or after treatment failure. During the transfusion independence response, white blood cell counts and platelet counts showed initial decreases in the first 2 months and then

were maintained at clinically acceptable levels. In the 51 out of 81 (75%) responders, treatment related grade 4 neutropenia and/or thrombocytopenia were resolved alongside the adjustment of the dose to a lower level (see **DOSAGE AND ADMINISTRATION**).

In the Phase 2 ITT population, major cytogenetic responses (complete resolution of all cytogenetic abnormalities compared with baseline) were observed in 44.2% (53/120) and minor cytogenetic responses (≥ 50% reduction in the proportion of hematopoietic cells with cytogenetic abnormalities compared with baseline) were observed in 24.2% (29/120) of the patients who were evaluable for cytogenetic response. Cytogenetic responses were assessed during the study at month 6, month 12 and when clinically indicated.

Among the 147 patients who had hematopoietic cells from bone marrow aspirate specimens available for cytogenetic testing, 110 (74.8%) had an MDS clone with an isolated del 5q cytogenetic abnormality, and 37 (25.2%) had an MDS clone with a del 5q abnormality and with additional cytogenetic abnormalities. Seventy-four (67%) of the 110 subjects with an isolated del 5q abnormality and 21 (57%) of the 37 subjects with a del 5q abnormality and an additional cytogenetic abnormality achieved RBC-transfusion independence.

Progression to Acute Myeloid Leukemia (AML)

In the Phase 3 study, the median duration of follow-up for all patients who received treatment with REVLIMID® regardless of randomized group, dose or study phase, was 35.2 months (2.9 years; range: 0.4, 70.8 months; n=194). Overall, the incidence of progression to AML during the entire study period was 30.2%. In all subjects who received REVLIMID®, the incidence of progression to AML or death was 59.8% (116/194 subjects).

The risk of progression to AML over time, taking the competing risk of death without AML into account, in the Phase 2 study (ITT population, N = 147) and Phase 3 study (subjects randomized to REVLIMID®, N = 138) is 0.146 and 0.152 at 2 years, 0.1741 and 0.2151 at 3 years, and 0.2216 and 0.2974 at 5 years (cumulative incidence function, Gray's test: p = 0.2259). In the Kaplan-Meier analysis of risk of progression to AML over time, the median time to progression to AML was 57 months in subjects randomized to placebo; the median time to progression to AML in subjects randomized to REVLIMID® had not been reached by the data cutoff date (30 Jun 2011). AML was defined as the presence of ≥ 30% bone marrow blasts according to FAB classification.

Patients without at least a minor erythroid response within 4 months of therapy initiation demonstrated by at least a 50% reduction in transfusion requirements or, if not transfused, a 1 g/dL rise in hemoglobin, should discontinue REVLIMID® treatment (see **DOSAGE AND ADMINISTRATION**, **Dosing Considerations**).

Multiple Myeloma

Phase 3 Randomized Open-Label Study in Transplant Non-Eligible Newly Diagnosed Multiple Myeloma

Study Demographics and Trial Design

A randomized, multicentre, open-label, 3-arm study [Study MM-020 (FIRST)] was conducted to evaluate the efficacy and safety of REVLIMID® and low-dose dexamethasone (Rd) given for 2 different durations of time [i.e., until disease progression (Arm Rd) or for up to eighteen 28-day cycles (Arm Rd18)], to that of melphalan, prednisone, and thalidomide (Arm MPT) for a maximum of twelve 42-day cycles (72 weeks) in the treatment of newly diagnosed multiple myeloma patients who were not eligible for stem cell transplant (SCT). Key eligibility criteria included patients with newly diagnosed, previously untreated, symptomatic multiple myeloma based on International Myeloma Working Group (IMWG) 2003 criteria. Patients were 65 years of age or older, or were younger but not candidates for SCT because they declined to undergo SCT or SCT was not available to the patient due to cost or other reasons, and had an ECOG performance status of 0-2. Patients were stratified at randomization by age (≤ 75 versus > 75), stage (ISS Stages I and II versus Stage III), and country.

Patients in Arm Rd and Arm Rd18 received REVLIMID® 25 mg once daily on days 1-21 of 28-day cycles. Dexamethasone was dosed 40 mg orally once weekly (in patients > 75 years of age, the dexamethasone dose was reduced to 20 mg once weekly) on days 1, 8, 15 and 22 of each 28-day cycle. Initial dose and regimens for Rd and Rd18 were adjusted according to age and renal function. All patients received prophylactic anticoagulation with the most commonly used being aspirin.

A total of 1623 patients were enrolled in the study. The baseline patient and disease-related characteristics of the patients were balanced among the 3 arms (see Table 10).

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 an Independent Response Adjudication Committee (IRAC) based on IMWG criteria or death from any cause. The primary comparison was between Arm Rd and Arm MPT.

Table 10: Baseline Demographic and Disease-Related Characteristics (ITT Population)

	Arm Rd (N=535)	Arm Rd18 (N=541)	Arm MPT (N=547)
Patient Characteristic			
Age (years)			
Median	73	73	73
Min, Max	44, 91	40, 89	51, 92
Age Distribution[a] n (%)			
≤ 75 n (%)	349 (65.2)	348 (64.3)	359 (65.6)
> 75 n (%)	186 (34.8)	193 (35.7)	188 (34.4)
Sex n (%)			
Male	294 (55.0)	273 (50.5)	287 (52.5)
Female	241 (45.0)	268 (49.5)	260 (47.5)
Race / Ethnicity n (%)			
White	474 (88.6)	480 (88.7)	491 (89.8)
Other	61 (11.4)	61 (11.3)	56 (10.2)
Disease Characteristic			
ISS Stage[b]			
I or II	319 (59.6)	322 (59.5)	323 (59.0)
III	216 (40.4)	219 (40.5)	224 (41.0)
Creatinine Clearance[a]			
< 30 mL/min	45 (8.4)	47 (8.7)	55 (10.1)
≥ 30 to 50 mL/min	126 (23.6)	120 (22.2)	126 (23.0)
≥ 50 to 80 mL/min	241 (45.0)	252 (46.6)	222 (40.6)
≥ 80 mL/min	123 (23.0)	122 (22.6)	144 (26.3)
ECOG Performance Status			
Grade 0	155 (29.0)	163 (30.1)	156 (28.5)
Grade 1	257 (48.0)	263 (48.6)	275 (50.3)
Grade 2	119 (22.2)	113 (20.9)	111 (20.3)
Grade ≥ 3	2 (0.4)	2 (0.4)	2 (0.4)
Missing	2 (0.4)	0 (0.0)	3 (0.5)
Cytogenetic Risk[b]			
Adverse risk	170 (31.8)	185 (34.2)	189 (34.6)
Non-Adverse Risk	298 (55.7)	290 (53.6)	283 (51.7)
Favourable hyperdiploidy	112 (20.9)	103 (19.0)	102 (18.6)
Normal	148 (27.7)	131 (24.2)	141 (25.8)
Uncertain Risk	38 (7.1)	56 (10.4)	40 (7.3)
Not Evaluable	34 (6.4)	35 (6.5)	44 (8.0)
Missing	33 (6.2)	31 (5.7)	31 (5.7)
B2-microglobulin			
> 5.5 mg/L	224 (41.9)	224 (41.4)	234 (42.8)
≤ 5.5 mg/L	309 (57.8)	316 (58.4)	312 (57.0)
Missing	2 (0.4)	1 (0.2)	1 (0.2)

[a]Subjects were stratified at randomization by: age, ISS stage, and renal status

[b]Cytogenetic risk categories are mutually exclusive. Definitions: Adverse Risk category: t(4;14), t(14;16), del(13q) or monosomy 13, del(17p), 1q gain; Non-adverse Risk categories include favourable hyperdiploidy: t(11;14), gains of 5/9/15; normal: a normal result, gains other than 5/9/15, IgH deletion; and uncertain risk: probes used for analysis cannot place subject in any of the other risk categories. Not evaluable: no specimen received, test failure, or insufficient number of cells available for analysis.

Study Results

The final analysis of PFS, the primary endpoint with 24 May 2013 data cutoff, was conducted on 960 events (59% of the ITT population). The PFS was significantly longer in Arm Rd than in Arm MPT: HR 0.72 (95% CI: 0.61, 0.85 p <0.0001) (see table 11 and Figure 1).

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 Arm Rd versus Arm MPT (95% CI: 0.62, 0.90) (see Table 11).

Table 11: Summary of Efficacy Results (ITT Population)

Trial Parameter	Arm Rd (N=535)	Arm Rd18 (N=541)	Arm MPT (N=547)
PFS – IRAC (months)[f]			
Number of PFS events, n(%)	278 (52.0)	348 (64.3)	334 (61.1)
Median[a] PFS time, months (95% CI)[b]	25.5 (20.7, 29.4)	20.7 (19.4, 22.0)	21.2 (19.3, 23.2)
HR (95% CI)[c]; p-value[d]			
Rd vs. MPT	0.72 (0.61, 0.85); < 0.0001		
Rd vs. Rd18	0.70 (0.60, 0.82); < 0.0001		
Rd18 vs. MPT	1.03 (0.89, 1.20); 0.7035		
Overall Survival – Interim (months)[g]			
Number of death events	208 (38.9)	228 (42.1)	261 (47.7)
Median[a] OS time, months (95% CI)[b]	58.9 (56.0, NE)	56.7 (50.1, NE)	48.5 (44.2, 52.0)
HR (95% CI) [c]			
Rd vs. MPT	0.75 (0.62, 0.90)		
Rd vs. Rd18	0.91 (0.75, 1.09)		
Rd18 vs. MPT	0.83 (0.69, 0.99)		
Myeloma Response Rate[e] – IRAC, n (%)[f]			
CR	81 (15.1)	77 (14.2)	51 (9.3)
VGPR	152 (28.4)	154 (28.5)	102 (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)
Duration of Response-IRAC (months)[f]			
Median[a] DOR (95% CI) [b]	35.0 (27.9, 43.4)	22.1 (20.3, 24.0)	22.3 (20.2, 24.9)

CI = confidence interval; CR = complete response; d = low-dose dexamethasone; HR = hazard ratio; IRAC = Independent Response Adjudication Committee; M = melphalan; NE = not evaluable; OS = overall survival; P = prednisone; PFS = progression free survival; PR = partial response; R = REVLIMID; Rd = 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% CI about the median

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

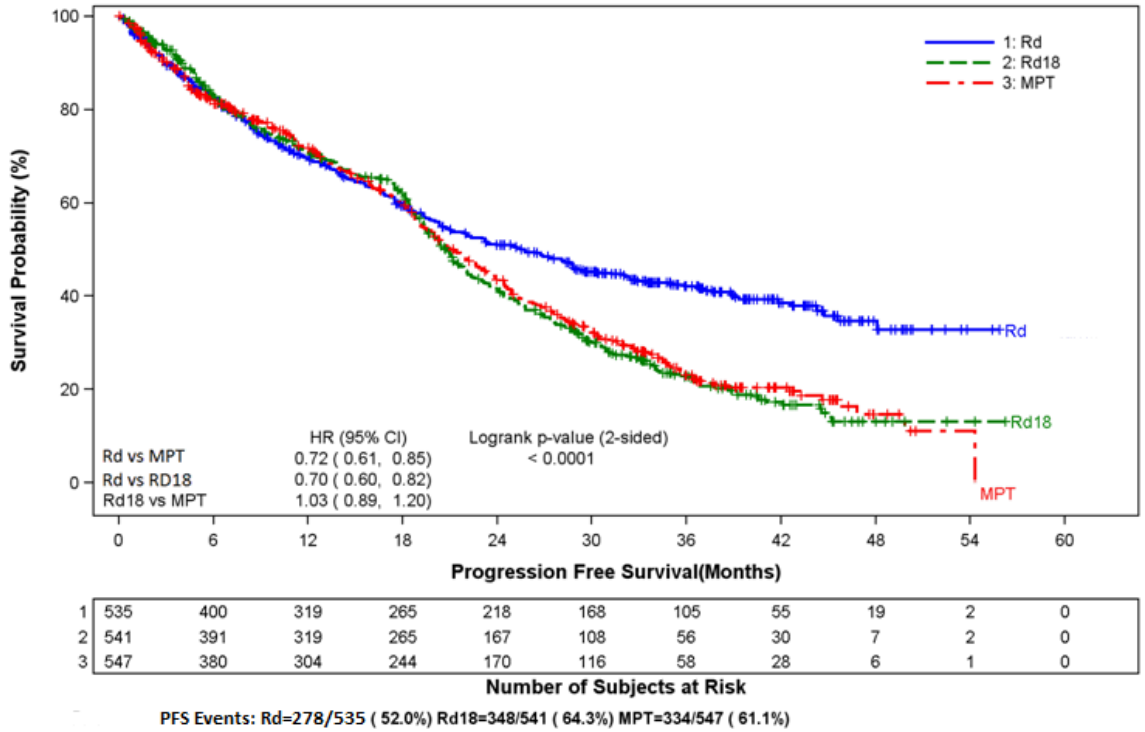
[d] The p-value is based on the unstratified log-rank test of Kaplan-Meier curve differences between the indicated arms

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

[f] Data cutoff date = 24 May 2013

[g] Data cutoff date = 3 March 2014

Figure 1: Kaplan-Meier Curves of Progression-free Survival from Study MM -020[a] Between Arm Rd, Arm Rd18 and Arm MPT (ITT Population) Cutoff date: 24 May 2013



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

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

[a] Based on IRAC Assessment

Phase 3 Randomized Double Blind Placebo-Controlled Studies in Previously Treated Multiple Myeloma Patients

Two randomized studies (Study MM-009 and MM-010) were conducted to evaluate the efficacy and safety of REVLIMID® in multiple myeloma subjects who had received at least one prior therapy. These multi-center, multi-national, double-blind, placebo-controlled studies compared REVLIMID® plus oral pulse high-dose dexamethasone therapy (REVLIMID®/dexamethasone) to dexamethasone therapy alone (placebo/dexamethasone), in subjects with MM who had received at least one prior treatment.

In both studies, subjects 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. Subjects in the placebo/dexamethasone group took 1 placebo capsule on Days 1 to 28 of each 28-day cycle. Subjects 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.

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**).

Table 12 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 12: Baseline Demographic and Disease-Related Characteristics

	MM-009 (Cutoff: 28 Jun 2005)		MM-010 (Cutoff: 03 Aug 2005)	
	REVLIMID®/ dexamethasone (N=177)	**PLACEBO/ dexamethasone (N=176)**	**REVLIMID® /dexamethasone (N=176)**	**PLACEBO/ dexamethasone (N=175)**
Patient Characteristics				
Age (years)				
Median	64.0	62.0	63.0	64.0
Min, Max	36.0, 86.0	37.0, 85.0	33.0, 84.0	40.0, 82.0
Sex				
Male	106 (59.9%)	104 (59.1%)	104 (59.1%)	103 (58.9%)
Female	71 (40.1%)	72 (40.9%)	72 (40.9%)	72 (41.1%)
Race/Ethnicity				
White	141 (79.7%)	148 (84.1%)	172 (97.7%)	175 (100.0%)
Other	36 (20.3%)	28 (15.9%)	4 (2.3%)	0 (0%)
ECOG Performance Status 0-1	157 (88.7%)	168 (95.5%)	150 (85.2%)	144 (82.3%)
Disease Characteristics				
Baseline Multiple Myeloma Stage [b]				
I	6 (3.4%)	5 (2.8%)	11 (6.3%)	8 (4.6%)
II	56 (31.6%)	55 (31.3%)	50 (28.4%)	57 (32.6%)
III	114 (64.4%)	116 (65.9%)	115 (65.3%)	110 (62.9%)
Missing	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)

	MM-009 (Cutoff: 28 Jun 2005)		MM-010 (Cutoff: 03 Aug 2005)	
	REVLIMID®/ dexamethasone (N=177)	**PLACEBO/ dexamethasone (N=176)**	**REVLIMID® /dexamethasone (N=176)**	**PLACEBO/ dexamethasone (N=175)**
Median (min, max) Baseline β_2-microglobulin levels (mg/L)	3.65 (1.1, 45.0)	3.30 (1.3, 15.2)	3.35 (1, 14.4)	3.25 (1.3, 25.3)
Number of Prior Therapies				
No. of Prior Antimyeloma Therapies 1 ≥ 2	 68 (38.4%) 109 (61.6%)	 67 (38.1%) 109 (61.9%)	 56 (31.8%) 120 (68.2%)	 57 (32.6%) 118 (67.4%)
Types of Prior Therapies				
Stem Cell Transplantation	61.0%	60.2%	56.3%	53.7%
Thalidomide	41.8%	45.5%	30.1%	38.3%
Dexamethasone	80.8%	70.5%	65.9%	68.6%
Bortezomib	10.7%	11.4%	4.5%	4.0%
Melphalan	33.3%	30.7%	56.3%	52.0%
Doxorubicin	54.8%	51.1%	55.7%	56.6%

[a] More than one category could be selected. Therefore, percentages may total to more than 100%.
[b] Baseline multiple myeloma stage was determined based on the Durie-Salmon staging criteria.

The efficacy and safety of the treatments were monitored at clinic visits that were scheduled at screening/baseline (within 28 days of Day 1 of Cycle 1), on Days 1, 8, and 15 of Cycle 1, on Days 1 and 15 of Cycles 2 and 3, on Day 1 of each subsequent cycle, and at treatment discontinuation. After discontinuation from the study, subjects are contacted every 6 months to obtain data on survival, the cause of death, and subsequent antimyeloma therapy.

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 or death due to progressive disease. The secondary efficacy endpoints were the myeloma response rate; the time to the first symptomatic skeletal-related event (SRE); the time to the first decrease in the ECOG performance status; and overall survival (OS). The response to therapy was assessed using the Myeloma Response Determination Criteria. The time to SRE was not analyzed due to the small number of observations available.

The median durations of observation at the time of the pre-planned analyses were 17 months for Study MM-009 and 16.5 months for Study MM-010.

Results

Protocol-specified Analysis of TTP (Primary Endpoint)

In both studies, TTP was significantly longer in the REVLIMID®/dexamethasone group than in the placebo/dexamethasone group ($p < 0.001$).

At the time of the preplanned interim analysis, the predetermined stopping criteria for superiority in the primary efficacy endpoint, TTP (as defined in the protocol), had been surpassed, with $p<0.001$ in favor of the REVLIMID®/dexamethasone treatment group. Both studies showed that the combination of REVLIMID®/dexamethasone was significantly superior to dexamethasone alone for TTP.

Subjects in the placebo/dexamethasone group were permitted to receive treatment with the REVLIMID®/dexamethasone combination after unblinding.

Table 13: Summary of Time to Progression

		MM-009 (Cutoff: 28 Jun 2005)		MM-010 (Cutoff: 03 Aug 2005)	
		REVLIMID®/ dexamethasone	PLACEBO/ dexamethasone	REVLIMID®/ dexamethasone	PLACEBO/ dexamethasone
	Statistics	(N=177)	(N=176)	(N=176)	(N=175)
TTP [a]	N	177	176	176	175
Progressed	n (%)	92 (52.0)	132 (75.0)	82 (46.6)	142 (81.1)
Censored	n (%)	85 (48.0)	44 (25.0)	94 (53.4)	33 (18.9)
Overall TTP (wk)	Median [b]	48.1	20.1	48.7	20.1
	[95% CI] [c]	[36.9, 61.4]	[16.7, 23.1]	[40.9, 72.1]	[18.1, 20.7]
	Mean [b]	39.0	20.6	38.0	22.9
	SD	28.55	19.17	27.08	19.03
	Min, Max	0.0, 106.9	0.0, 93.1	0.1, 93.4	0.3, 90.1
Hazard Ratio [95% CI] [d]		0.354 [0.270, 0.466]		0.351 [0.266, 0.463]	
Log-rank Test p-Value [e]		< 0.001		< 0.001	

NE, not estimable

[a] Time to progression was calculated as the time from randomization to the first occurrence of any of the following events: 1) disease progression based on the myeloma response criteria developed by Bladé et al, 2) discontinuation from the treatment phase due to disease progression according to the investigator whether or not confirmed by the Bladé et al criteria (TTP was measured to the last date of visit), or death due to disease progression during the treatment period (TTP was measured to the date of death if death occurred on or before treatment discontinuation). The TTP was censored at the date of the last response assessment for subjects who 1) had not progressed at the time of the analysis, 2) withdrew from the treatment phase before documented progression, including those who died of causes not related to multiple myeloma, or 3) were given another antimyeloma therapy without documented progression or experienced intolerable adverse events (for these subjects, the date of their last response assessment prior to taking other antimyeloma therapy was used as the censor date).

[b] The median is based on the Kaplan-Meier estimate, and the mean is the univariate mean without adjusting for censoring (i.e., the mean values represent mean TTP documented to date as of the data cutoff date, without consideration of the fact that a substantial number of subjects who had not yet progressed were continuing in the study).

[c] Ninety-five percent confidence interval (CI) about the median overall TTP

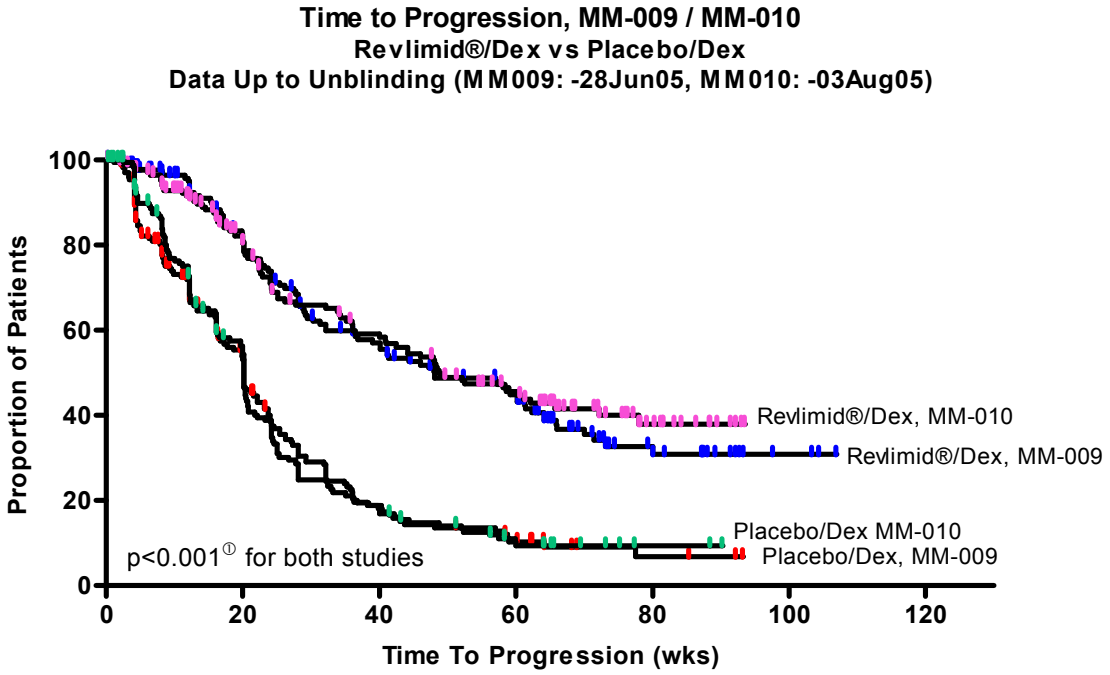
[d] Based on a proportional hazards model comparing the hazard functions associated with the treatment groups (REVLIMID®/dexamethasone:placebo/dexamethasone)

[e] The p-value is based on a 2-tailed unstratified log-rank test of survival curve differences between the treatment groups.

Superiority of REVLIMID®/dexamethasone over placebo/dexamethasone was also observed regardless of gender, age (≤ 65 years and > 65 years), prior therapy (with high-dose chemotherapy and SCT or without such therapy), or the number of prior antimyeloma regimens (1 vs > 1).

Figure 2 depicts the Kaplan-Meier estimates of TTP as of the dates on which the studies were unblinded.

Figure 2: Kaplan-Meier Estimate of Time to Progression



① p-value from log-rank test

Progression Free Survival (PFS) - Sensitivity Analysis)

The analysis of PFS, which differed from the protocol-specified primary TTP analysis in that all deaths, regardless of causality, were considered as events confirmed the results that were observed with the protocol-specified analysis of TTP. Highly significant differences between treatment groups ($p < 0.001$) in favor of the REVLIMID®/dexamethasone combination, were observed in both studies (see Table 14).

Table 14: Summary of Progression-free Survival (Sensitivity Analysis)

		MM-009 (Cutoff: 28 Jun 2005)		MM-010 (Cutoff: 03 Aug 2005)	
	Statistics	REVLIMID®/ dexamethasone (N=177)	PLACEBO/ dexamethasone (N=176)	REVLIMID®/ dexamethasone (N=176)	PLACEBO/ dexamethasone (N=175)
PFS [a] Time	N	177	176	176	175
Progressed	n (%)	93 (52.5)	134 (76.1)	95 (54.0)	148 (84.6)
Censored	n (%)	84 (47.5)	42 (23.9)	81 (46.0)	27 (15.4)
Overall PFS (wk)	Median [b]	48.0	20.1	44.1	20.1
	[95% CI] [c]	[36.9, 61.4]	[16.4, 23.1]	[34.3, 59.0]	[16.1, 20.4]
	Mean [b]	39.1	20.6	37.7	22.9
	SD	28.52	19.16	27.11	19.01
	Min, Max	0.0, 106.9	0.0, 93.1	0.1, 93.4	0.3, 90.1
Hazard Ratio [95% CI] [d]		2.820 [2.148, 3.701]		2.459 [1.891, 3.199]	
Log-rank Test p-Value [e]		< 0.001		< 0.001	

NE, not estimable

[a] Calculated as the time from randomization to documented progression or death due to any cause, whichever occurred first. If withdrawal due to adverse events or change of therapy occurred before documented progression or death, then these observations were censored at the last progression assessment date.

[b] The median is based on the Kaplan-Meier estimate, and the mean is the univariate mean without adjusting for censoring (i.e., the mean values represent mean PFS documented to date as of the data cutoff date, without consideration of the fact that a substantial number of subjects who had not yet progressed were continuing in the study).

[c] Ninety-five percent confidence interval (CI) about the median overall PFS.

[d] Based on a proportional hazards model comparing the hazard functions associated with the treatment groups (REVLIMID®/dexamethasone:placebo/dexamethasone)

[e] The p-value is based on a 1-tailed unstratified log-rank test of survival curve differences between the treatment groups.

Myeloma Response Rate (Secondary Endpoint)

In both studies, the myeloma response rates were significantly higher in the REVLIMID®/dexamethasone group than in the placebo/dexamethasone group both for the overall comparison of response categories ($p < 0.001$) and for the dichotomous comparison of Complete Response (CR) + Remission Response (RR) + Partial Response (PR)(($p < 0.001$) (see Table 15). The overall response rates in Study 009 were consistent with those in Study 010, with 61.0% (108/177) of the REVLIMID®/dexamethasone-treated subjects in Study 009 and 60.2% (106/176) of the REVLIMID®/dexamethasone-treated subjects in Study 010 achieving a CR, RR plus PR.

Table 15: Summary of Myeloma Response Rates Based on Best Response Assessments (Studies MM-009 and MM-010)

Response [a, b]	Study MM-009 (Cutoff: 28 Jun 2005)		Study MM-010 (Cutoff: 03 Aug 2005)	
	REVLIMID®/ dexamethasone (N=177)	PLACEBO/ dexamethasone (N=176)	REVLIMID®/ dexamethasone (N=176)	PLACEBO/ dexamethasone (N=175
Complete Response (CR)	25 (14.1%) [g]	1 (0.6%)	28 (15.9%) [g]	6 (3.4%)
Partial Response (PR)	31 (17.5%)	18 (10.2%)	32 (18.2%)	20 (11.4%)
Stable Disease (SD)	54 (30.5%)	102 (58.0%)	53 (30.1%)	97 (55.4%)
Progressive Disease (PD)	5 (2.8%)	25 (14.2%)	3 (1.7%)	25 (14.3%)
Not Evaluable (NE) [c]	10 (5.6%)	14 (8.0%)	14 (8.0%)	11 (6.3%)
p-value [d]	< 0.001		< 0.001	
Dichotomized Response				
CR, RR, or PR	108 (61.0%)	35 (19.9%)	106 (60.2%)	42 (24.0%)
SD, PD, or NE	69 (39.0%)	141 (80.1%)	70 (39.8%)	133 (76.0%)
p-value [e]	< 0.001		< 0.001	
Odds Ratio [f] [95% CI]	6.31 [3.91, 10.17]		4.80 [3.03, 7.59]	

[a] Response is based on the review of all myeloma assessment data using Bladé et al criteria.
[b] Response is the highest assessment of response during the treatment phase of the study.
[c] Includes subjects who did not have any response assessment data as of the data cutoff date and those whose only assessment was "response not evaluable." This category was not included in the Wilcoxon rank sum test.
[d] Probability from Wilcoxon rank sum test
[e] Probability from continuity-corrected Pearson chi square test
[f] Odds ratio (REVLIMID®:placebo)
[g] Significantly higher in the REVLIMID®/dexamethasone group than in the placebo/dexamethasone group ($p < 0.003$, continuity-corrected Pearson chi square test)

Based on subgroup analyses, the myeloma response rate (CR + RR + PR) and CR rate were significantly higher in the REVLIMID®/dexamethasone group than in the placebo/dexamethasone group regardless of gender, age (≤ 65 years or > 65 years), prior therapy (with high-dose chemotherapy and SCT or without such therapy; or number of prior antimyeloma regimens (1 vs ≥ 1). The myeloma response rate (CR + RR + PR) and the CR rate were also significantly higher in the REVLIMID®/dexamethasone group than in the placebo/dexamethasone group both in subjects who had a baseline serum β2-microglobulin level of ≤ 2.5 mg/L and in those who had a baseline β2-microglobulin level of > 2.5 mg/L.

Overall Survival (Secondary endpoint)

Based on pooled data from Study 009 and Study 010 at the time of un-blinding, overall survival (OS) was significantly longer ($p<0.001$); among the REVLIMID®/dexamethasone-treated subjects than among the placebo/dexamethasone -treated subjects. Subjects in the placebo/dexamethasone group were permitted to receive treatment with the REVLIMID®/dexamethasone combination after un-blinding. As of January 2007, OS was significantly longer ($p=0.015$) among the REVLIMID®/dexamethasone-treated subjects than among the placebo/dexamethasone -treated subjects (see Table 16), however the data are confounded by the effects of the crossover of placebo/dexamethasone subjects to REVLIMID®. A total of 146 patients (96 from Study MM-009 and 50 from Study MM-010) rolled over to receive REVLIMID® before study un-blinding. After study un-blinding, a total of 19 patients (5 from Study MM-009 and 14 from Study MM-010) crossed over to receive REVLIMID®/dexamethasone.

Table 16: Summary of Overall Survival as of January 2007: Intent-To-Treat Population

Overall Survival (OS) Statistics	**Pooled Data**	
	REVLIMID®/ dexamethasone N=353	**PLACEBO/ dexamethasone N=351**
Died n (%)	152 (43.1)	180 (51.3)
Median OS time since randomization, weeks [a]	149.7	133.3
95% CI [b]	[141.6, NE]	[111.0, 151.7]
Mean ± SD	101.5 ± 51.39	92.4 ± 53.86
Min, Max	1.1, 183.1	0.0, 187.9
Hazard rate ratio [c]	0.765 [0.616, 0.949]	
p-value [d]	0.015	
3-yr survival rate (95% CI)	47% (40-54%)	43% (37-49%)

Notes: The median in this table is based on Kaplan-Meier estimate, and the mean is the univariate mean without adjusting for censoring.

NE= Not Estimable

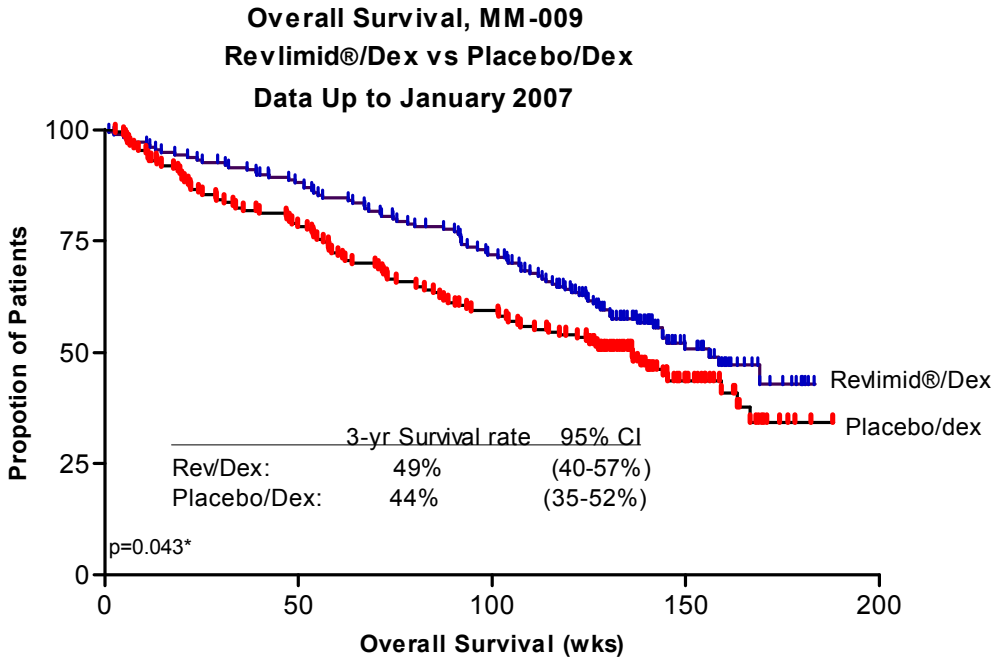
[a] For subjects who died during the follow-up phase and whose death dates are not available, the follow-up visit dates are used as the event date.

[b] 95% confidence intervals about the median survival time.

[c] Based on a proportional hazards model comparing the hazard functions associated with the treatment groups (REVLIMID®/dexamethasone: Placebo/dexamethasone)

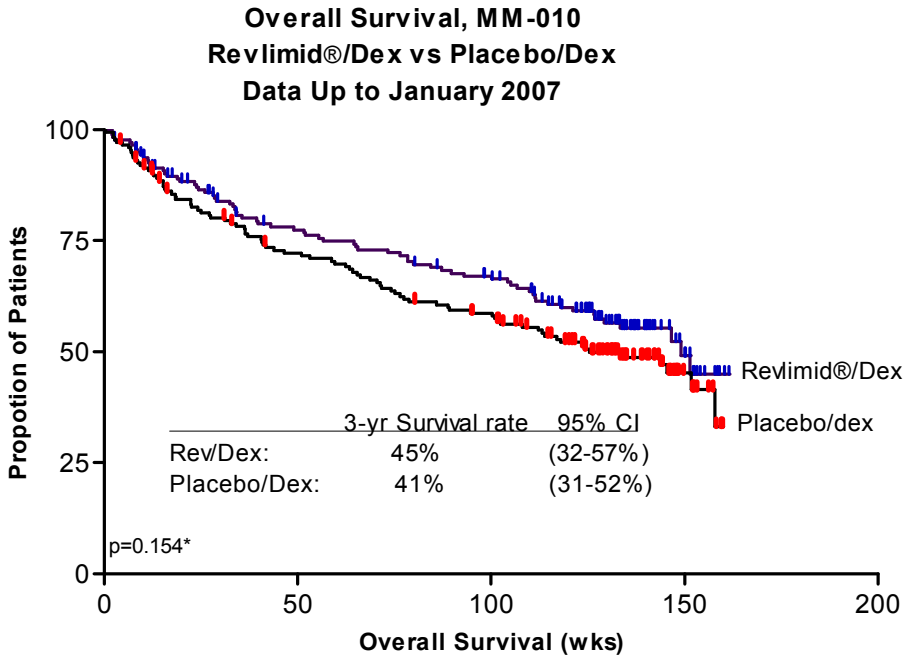
[d] The p-value is based on a two-tailed unstratified log rank test of survival curve differences between the treatment groups.

Figure 3: Overall Survival Data from CC-5013-MM-009; January 2007



*p-value from log-rank test

Figure 4: Overall Survival Data from CC-5013-MM-010; January 2007



*p-value from log-rank test

Time to First Worsening of ECOG Performance Status (Secondary Endpoint)

The time to the first worsening of the ECOG performance status score was significantly longer for the REVLIMID®/dexamethasone-treated subjects than for the placebo/dexamethasone-treated subjects in Study 009 (p = 0.012). No significant difference in the time to first worsening in the ECOG performance status score was observed between the REVLIMID®/dexamethasone and placebo/dexamethasone groups in Study 010.

Bioavailability Studies

A randomized, open label, two-way crossover study was conducted comparing the bioavailability of single 10 mg doses of lenalidomide, administered as 4 × 2.5 mg capsules or as 2 × 5 mg Revlimid® capsules. The study was conducted in 27 healthy adult male subjects, under fasting conditions.

Table 17: Summary Table of the Comparative Bioavailability Data

Lenalidomide
10 mg
From measured data

Geometric Mean
Arithmetic Mean (CV%)

Parameter	4 × 2.5 mg Revlimid® Capsule (Test)	2 × 5 mg Revlimid® Capsules (Reference)*	% Ratio of Geometric Means	90% Confidence Interval
AUC_t (ng•h/mL)	541.30 548.82 (17.4)	528.99 537.90 (18.9)	101.65	98.46 – 104.93
AUC_∞ (ng•h/mL)	555.09 561.89 (16.5)	547.23 555.10 (17.5)	100.80	97.85 – 103.84
C_{max} (ng/mL)	171.59 176.26 (23.7)	169.17 176.58 (30.8)	101.83	92.70 – 111.87
T_{max} § (h)	0.75 (0.50 – 2.50)	0.75 (0.50 – 1.50)		
$T_{1/2}$ † (h)	3.54 (19.4)	3.39 (19.3)		

*Revlimid® (lenalidomide) 5 mg capsules, Celgene Inc., Canada
§Expressed as the median (range) only
†Expressed as the arithmetic mean (CV%) only

A randomized, open label, two-way crossover study was conducted comparing the bioavailability of single 20 mg doses of lenalidomide, administered as 1 x 20 mg REVLIMID® capsules or as 4 x 5 mg REVLIMID® capsules. The study was conducted in 28 healthy male subjects, under fasting conditions.

Table 18: Summary of the Comparative Bioavailability Data				
Lenaliomide 20 mg From measure data Geometric Mean Arithmetic Mean (CV%)				
Parameter	**1 x 20 mg Revlimid® Capsule (Test)**	**4 x 5 mg Revlimid® Capsules (Reference)***	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_t (ng•h/mL)	1046.95 1059 (15.6)	1025.77 1037 (15.5)	102.07	99.77 – 104.41
AUC_∞ (ng•h/mL)	1089.40 1102 (16.0)	1061.57 1074 (15.7)	102.62	99.98 – 105.34
C_{max} (ng/mL)	321.64 330 (23.3)	310.22 321 (28.0)	103.68	96.57 – 111.31
T_{max}[a] (h)	0.89 (0.50 – 3.00)	0.75 (0.50 – 2.50)		
$T_{1/2}$[b] (h)	3.10 (11.7)	3.07 (12.4)		

*Revlimid (lenalidomide) 5 mg capsules, Celgene Inc., Canada
a Expressed as the median (range) only
b Expressed as the arithmetic mean (CV%) only

DETAILED PHARMACOLOGY

Clinical Pharmacokinetics

The pharmacokinetic profile of lenalidomide has been evaluated in Caucasian, Japanese, and Chinese patients with previously treated multiple myeloma (MM) (see Table 19).

Table 19: Single-dose Pharmacokinetic Parameters of Lenalidomide in Patients with Previously Treated MM

Parameter	Multiple Myeloma (Lenalidomide = 25 mg, Clcr ≥ 60 mL/min)		
	Caucasian[a] (N = 34)	**Japanese[a] (N = 12)**	**Chinese (N = 9)**
AUC_∞ (ng•h/mL)	2124 (28.6)	2305 (23.7)	2202 (30.6)
C_{max} (ng/mL)	487 (35.0)	572 (33.2)	596 (30.2)
T_{max} (h)	1.0 (0.4-4.0)	1.0 (0.4-2.0)	0.93 (0.5-1.0)
CL/F (mL/min)	196 (28.7)	181 (23.7)	184 (30.7)
$t_{1/2}$ (h)	3.18 (20.7)	2.70 (19.3)	3.18 (39.0)

Median (minimum – maximum) data are presented for T_{max} and geometric mean (CV%) data are presented for other parameters. Only patients with similar renal function (CLcr > 60 mL/min) are included.
AUC_∞ = AUC from time zero extrapolated to infinity; C_{max} = maximum concentration; CL/F = apparent total clearance ; $t_{1/2}$ = terminal half-life; T_{max} = time to reach C_{max}..
[a]AUC_∞ and C_{max} are normalized to the level at 25 mg.

Drug Interactions

The pharmacokinetics of lenalidomide (25 mg/day) when administered alone or in combination with dexamethasone (40 mg/day) was evaluated in Japanese and Chinese subjects with previously treated multiple myeloma (see Table 20). Dexamethasone had no effect on the pharmacokinetics of lenalidomide.

Table 20 Summary of Pharmacokinetic Parameters of Lenalidomide Alone or in Combination with Dexamethasone in Subjects with Previously Treated MM

Parameter	Japanese Subjects[a]		Chinese Subjects[b]	
	Len 25 mg Day 1 (N=6)	Len + Dex Day 12 (N=6)	Len 25 mg Day 7 (N=11)	Len + Dex Day 8 (N=10)
C_{max} (ng/mL)	474 (27.1)	433 (46.1)	478 (19.3)	494 (19.9)
t_{max} (h)	1.70 (1.00-1.97)	2.76 (0.53-4.0)	1.5 (0.5-3.1)	1.00 (0.50-2.98)
AUC_{τ} (ng· h/mL)	2177 (12.6)	1890 (17.4)	2117 (43.7)	2093 (41.2)
$t_{1/2}$ (h)	2.56 (14.0)	2.55 (23.0)	2.79 (32.6)	3.08 (46.8)
CL/F (mL/min)	191 (12.8)	221 (18.3)	195 (45.5)	193 (42.6)

Median (minimum-maximum) data are presented for Tmax and geometric mean (CV%) data are presented for other parameters. AUC = area under the concentration versus time curve from the time zero until the end of the dosing interval (τ=24); C_{max} = maximum concentration; CL/F = apparent total plasma clearance when dosed orally; $t_{1/2}$ = terminal half life

[a] Lenalidomide was administered at 25 mg daily on Days 1 and 3-12 and dexamethasone at 40 mg daily on Days 2-4 and 9-12.

[b] Lenalidomide was administered at 25 mg daily on Days 1-8 and dexamethasone at 40 mg on Day 8.

Non-Clinical Pharmacology

REVLIMID® (lenalidomide) is a potent and orally effective antineoplastic, immunomodulatory, and antiangiogenic drug. The pharmacological properties of lenalidomide were characterized in both in vitro and in vivo non-GLP studies examining the complex set of pathological conditions associated with myelodysplastic syndromes (MDS) and for the potential to produce any adverse secondary pharmacological effects. The results of these studies demonstrate that lenalidomide affects many biological processes associated with MDS. Specifically, lenalidomide induces fetal hemoglobin expression upon $CD34^+$ hematopoietic stem cell differentiation in a model of erythroid progenitor differentiation; inhibits proliferation of various hematopoietic tumor cell lines, in particular those with cytogenetic defects of chromosome 5 and multiple myeloma (MM) plasma tumor cells; and inhibits angiogenesis in vitro by blocking the formation of microvessels and endothelial cell tubes, as well as the migration and adhesion of endothelial cells and in vivo by reducing the microvessel density in the rat mesenteric window model and in the beige-nude-xid mouse MM tumor model. In addition, lenalidomide stimulates T-cell proliferation and interleukin (IL)-2 and interferon-gamma production; and increases natural killer (NK) and NK T cell number and activity; and inhibits the secretion of pro-inflammatory cytokines including tumor necrosis factor-alpha, IL-1β, IL-6 and IL-12, and increases the secretion of anti-inflammatory cytokine IL-10 from peripheral blood mononuclear cells.

Some of the cellular effects listed above (T cell stimulation, inhibition of tumor cell proliferation, and inhibition of endothelial cell migration) are associated with modulation of the Akt pathway, suggesting that this core signaling pathway may be a key molecular target of lenalidomide.

In rats and monkeys, lenalidomide is cleared at a moderate rate from the systemic circulation, and is rapidly absorbed, with oral bioavailability of ≥ 50% in rats and monkeys. In animals, systemic exposure increased with increasing doses, with no notable accumulation on multiple dosing of lenalidomide.

The plasma protein binding of lenalidomide is low (19 to 29% bound) in nonclinical species as well as humans. ^{14}C-Lenalidomide-derived radioactivity is extensively distributed into tissues in rats. Very limited distribution of radioactivity occurs into the central nervous system (less than 5% of levels in blood).

Lenalidomide is not subject to cytochrome P450 mediated metabolism in vitro. It undergoes hydrolysis in aqueous media, and animal and human plasma. The enantiomers of lenalidomide undergo facile interconversion in animal and human plasma in vitro.

The excretion of radioactivity following oral dosing of ^{14}C-lenalidomide to rats and monkeys is rapid and occurs *via* both the urine and feces. In both rats and monkeys, the major component of the excreted radioactivity is the parent compound (50 to 58% of the dose). The remaining radioactive dose is excreted as multiple metabolites comprising isomeric forms of hydrolytic metabolites (5 to 10% of the dose), an N-acetyl conjugate (less than 3% of the dose) and isomers of a glucose conjugate (less than 13% of the dose). Thus, multiple clearance mechanisms contribute to the overall elimination of lenalidomide in animal models.

Lenalidomide does not inhibit or induce cytochrome P450 isoforms in vitro, and hence is not likely to precipitate drug-drug interactions when administered with cytochrome P450 substrates. In vivo in both rats and monkeys, chronic administration of lenalidomide did not result in the induction of cytochrome P450 enzymes. In vitro lenalidomide is a weak substrate, but is not an inhibitor of P-glycoprotein. Hence clinically relevant drug-drug interactions between lenalidomide and P-glycoprotein substrates or inhibitors are unlikely.

Non-Clinical Safety Pharmacology

Results of safety pharmacology studies have shown that lenalidomide did not induce behavioral or autonomic changes when administered orally to male rats at doses up to 2000 mg/kg, did not produce major inhibition of the cloned human cardiac potassium channel (hERG) (IC_{50} > 786.7 μM) in vitro, and did not induce any biologically significant cardiovascular or respiratory changes when administered intravenously to anesthetized dogs at doses up to 20 mg/kg.

TOXICOLOGY

Study Title	Findings
Single dose intravenous toxicity study in the mouse	No deaths after a single intravenous administration of 40 mg/kg were observed in mice.
Single dose oral toxicity study in the mouse	No deaths after a single oral dose of 2000 mg/kg were observed in mice.
Single dose intravenous toxicity study in the rat	No deaths after a single intravenous administration of 40 mg/kg were observed in rats.
Single dose oral toxicity study in the rat	No deaths after a single oral dose of 2000 mg/kg were observed in rats.
7 day oral (gavage) range-finding toxicity study in the mouse	High dose females exhibited slightly elevated liver weights ($p<0.05$). NOAEL = 1000 mg/kg/day.
7 day oral (gavage) range finding toxicity study in the rat	Decreased red blood cell indices in treated males. Increased urea and creatinine in treated males at 500 and 2000 mg/kg. Increased kidney weights in males at 500 and 2000 mg/kg. NOAEL = < 500 mg/kg/day.
28 day oral (gavage) toxicity study in the rat	Bodyweight and feed consumption decreased in high dose males. Unidentified crystals were noted in the urine of treated animals. At week 4, increased incidence of proteinuria and hematuria in high dose males. White powder deposit was noted in the urine of the mid and high dose animals. Moderate to severe tubular necrosis or nephropathy noted in the high dose rats. Slight decrease in red blood cell parameters for high dose males. NOAEL = 300 mg/kg/day.
13 week oral (gavage) toxicity study in the rat	Decreased body weight gains and unidentified crystals in the urine at the mid and high dose. NOAEL = 75 mg/kg/day.
26 week (with a 4 week treatment-free recovery period) oral (gavage administration) toxicity study in the rat	Male and female rats were administered 0, 75, 150 or 300 mg/kg/day for 26 weeks. In this study, there were 3 non-treatment related deaths; 1 male at 300 mg/kg and 2 females from control and 150 mg/kg groups. No treatment-related clinical signs were observed during the treatment and treatment-free periods. Hematology, clinical chemistry, urinalysis, ophthalmoscopic findings were unaffected by treatment. At the end of treatment, there were slight decreases of 16% and 9% in group mean unadjusted liver weight and organ to body weight ratio in males dosed with 300 mg/kg/day. Microscopically, a treatment-related increase in the incidence of pelvic mineralization was seen in the kidney at all doses. After 4 weeks, recovery from this effect was observed in the high dose group. The NOAEL was 75 mg/kg/day.
28 day oral (gavage) toxicity study in the monkey.	One animal sacrificed in moribund condition. Animal exhibited increased urea, creatinine & bilirubin. Lesions in bone marrow & lymphocytic system, kidneys, GI tract & liver. Minor atrophy of the thymus, spleen and peripheral lymph nodes and altered hematopoiesis were noted. NOAEL was not achieved.
28 day oral (gavage) toxicity study in the monkey	No treatment related effects. NOAEL = 2 mg/kg/day.

Study Title	Findings
13 week oral (gavage) toxicity study in the monkey	The top dose of 2/mg/kg/day was the NOAEL. Evidence of pharmacodynamic activity was noted at all dose levels.
52 week oral (gavage administration) toxicity study in the monkey	A number of animals administered 4 and 6 mg/kg/day were terminated early due to toxicity on Day 135. In these animals, treatment-related findings consisted of severely reduced RBC, WBC, and platelet counts, hemorrhage in multiple organs, gastrointestinal tract inflammation and lymphoid and bone marrow atrophy. For animals administered 1 and 2 mg/kg/day, mild, but inconsistent, suppression of white blood cell count at 2 mg/kg/day was observed. Histology at 52 weeks showed atrophy of the thymus at both doses. After 7 weeks of recovery, platelet and WBC counts were similar to control; the effects on the thymus were partially reversed. The NOAEL in this study was 1 mg/kg/day.
Fertility and early Embryonic Development	A fertility and early embryonic development study in rats, with administration of lenalidomide up to 500 mg/kg, produced no parental toxicity and no adverse effects on fertility.
Embryo-fetal development studies:	Embryofetal developmental toxicity studies were conducted in rats, rabbits and monkeys. In monkeys, malformations were observed in the offspring of female monkeys who received lenalidomide doses as low as 0.5 mg/kg/day during pregnancy. Exposure in monkeys at this dose (AUC of 378 ng•hr/mL) was 0.17-times the exposure from a human clinical dose of 25 mg/day (AUC of 2215 ng•hr/mL). The observed malformations ranged from stiff and slightly malrotated hindlimbs at 0.5 mg/kg/day lenalidomide up to severe external malformations, such as bent, shortened, malformed, malrotated, and/or absent part of the extremities, oligo– or polydactyly at 4 mg/kg/day lenalidomide. These external malformations had correlated skeletal finding and were similar to those seen with the positive control thalidomide treatment. In rabbits, the maternal and developmental NOAELs for lenalidomide were 3 mg/kg/day. Exposure of rabbits at this dose (AUC of 2858 ng•hr/mL) was 2.3 fold higher than in patients administered 10 mg of lenalidomide based on AUC. Exposure in patients administered 25 mg of lenalidomide was approximately the same as in rabbits at the NOAEL dose based on AUC. Lenalidomide has been shown to have an embryocidal effect in rabbits at a dose of 50 mg/kg. Developmental toxicity at the 10 and 20 mg/kg/day dose levels was characterized by slightly reduced fetal body weights, increased incidences of post implantation loss, and gross external findings in the fetuses associated with morbidity and pharmacotoxic effects of lenalidomide (purple discoloration of the skin on the entire body).

Study Title	Findings
Pre- and Post-Natal Development:	A pre- and post-natal development study in rats revealed few adverse effects in the offspring of female rats treated with lenalidomide at doses up to 500 mg/kg (approximately 600 times and 240 times the human dose of 10 and 25 mg, respectively based on body surface area). Exposures to lenalidomide at these doses were ≥ 128-fold and 50-fold higher than in patients administered 10 mg and 25 mg, respectively based on AUC. The male offspring exhibited slightly delayed sexual maturation, and the female offspring had slightly lower body weight gains during gestation when bred to male offspring.
Carcinogenicity	Carcinogenicity studies with lenalidomide have not been conducted.
Mutagenicity	Lenalidomide did not induce mutation in the Ames test, chromosome aberrations in cultured human peripheral blood lymphocytes, or mutation 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.

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PrREVLIMID®

lenalidomide capsules

PART III: CONSUMER INFORMATION

MYELODYSPLASTIC SYNDROMES

This leaflet is part III of a three-part "Product Monograph" published when REVLIMID® (lenalidomide) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about REVLIMID®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

REVLIMID® can only be given to patients who are registered in and meet all conditions of the RevAid® program. RevAid® is a controlled distribution program of REVLIMID®.

What the medication is used for:

REVLIMID® is used in the treatment of patients who require blood transfusions due to myelodysplastic syndromes (MDS) with a chromosome problem in which part of chromosome 5 is missing. This type of MDS is known as deletion 5q MDS.

What it does:

The details of how REVLIMID® works in deletion 5q MDS are still being studied. When patients with deletion 5q MDS are treated with REVLIMID®, abnormal cells in their bone marrow are often eliminated and replaced by normal-appearing cells. REVLIMID® can also directly stimulate the production of red blood cells by the bone marrow. These effects can improve anemia, and reduce or eliminate the need for transfusions in patients with MDS.

When it should not be used:

Do not take REVLIMID® if:

- You are pregnant
- You are at risk of becoming pregnant
- You become pregnant during REVLIMID® treatment
- You are breastfeeding
- You are a male patient and are unable to follow or comply with the contraceptive measures of the RevAid Program
- **REVLIMID® can cause an increased risk of death in people who have chronic lymphocytic leukemia (CLL).** Do not take REVLIMID® if you have CLL unless you are participating in a controlled clinical trial.
- REVLIMID® treatment should not be started in patients whose platelet levels are less than 50 x 10^9/L.
- You are allergic to lenalidomide, pomalidomide or thalidomide or any of the other ingredients in REVLIMID®. REVLIMID® contains lactose.

What the medicinal ingredient is:

lenalidomide

What the important nonmedicinal ingredients are:

Each capsule contains croscarmellose sodium, lactose anhydrous, magnesium stearate, and microcrystalline cellulose. The additional composition of the different capsule strengths is provided in the table below.

Strength	Imprint	Composition	Colour	Package size
5 mg	REV, 5 mg	Gelatin, titanium dioxide	White opaque	28 count blisters
10 mg	REV, 10 mg	FD&C blue #2, gelatin, titanium dioxide, yellow iron oxide	Blue/green opaque and pale yellow opaque	28 count blisters

What dosage forms it comes in:

Capsules. Each capsule contains 5 mg or 10 mg lenalidomide.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

REVLIMID® should only be prescribed by a doctor experienced in the use of anti-cancer drugs and registered with the RevAid® controlled distribution program.

Serious side effects may occur with the use of REVLIMID® and could include:

- birth defects (deformed babies) or death of an unborn baby and spontaneous abortion;
- decrease in the production of blood cells resulting in very low levels of white blood cells (neutropenia) and of platelets (thrombocytopenia);
- blood clots in the veins (Deep Vein Thrombosis), in the lung (Pulmonary Embolism), and in the arteries (heart attacks and stroke). Use of a blood thinner medication is recommended to reduce the risk;
- Liver problems. Treatment with REVLIMID® may lead to a higher risk of liver problems which may cause death.

REVLIMID® is only available under a controlled distribution program called RevAid®.

BEFORE you use REVLIMID® talk to your doctor or pharmacist if you:

- are pregnant or are planning to get pregnant
- are breastfeeding
- have kidney problems
- have liver problems
- have blood problems
- have or have had heart problems (irregular heart beat, heart attack)
- smoke, have high blood pressure or high cholesterol levels
- have had previous viral infection including herpes zoster infection (shingles) and/or hepatitis B virus infection (a viral infection of the liver)

REVLIMID® may cause birth defects. In order to take this drug you must meet the following conditions:

1. Females who can get pregnant:

- Discuss contraception (birth control) with your healthcare provider.
- Use at least two effective methods of contraception at the same time.
- Use these two effective methods of contraception:
  - For at least 4 weeks before starting REVLIMID® treatment
  - During interruptions of REVLIMID® treatment
  - During REVLIMID® treatment
  - For at least 4 weeks after stopping REVLIMID® treatment
- You must have two negative pregnancy tests before starting treatment:
  - The first 7-14 days prior to starting treatment
  - The second within 24 hours of starting treatment.
- You must have negative pregnancy tests during treatment:
  - Once weekly for the first 4 weeks
  - Once every 4 weeks (or once every 2 weeks if your period is irregular) for the duration of treatment and during treatment interruption
- You must have a final pregnancy test 4 weeks after stopping REVLIMID®.

2. Males:

- REVLIMID® is present in the sperm of males who take this drug. Use a condom every time you have sexual intercourse with a woman who is pregnant or can get pregnant. This must be done even if you have undergone a successful vasectomy. The condom must be used while:
  - You are taking REVLIMID®
  - During interruptions of treatment
  - For 4 weeks after stopping REVLIMID®.
- Do not donate sperm while taking REVLIMID® and for 4 weeks after stopping REVLIMID®.
- Inform your sexual partner who can get pregnant that:
  - You are taking REVLIMID®
  - There is a risk of birth defects, stillbirths, and spontaneous abortions if a fetus is exposed to your sperm.
  - You must use a condom.

You should contact your doctor immediately if you think your female partner becomes pregnant while you are taking REVLIMID®.

3. All Patients:

REVLIMID® may cause birth defects and any method of birth control can fail. You should contact your doctor immediately if you think you or your female partner may be pregnant. You should also contact your doctor if you miss your period or experience unusual menstrual bleeding.

- Do not give blood while you take REVLIMID® and for 4 weeks after stopping REVLIMID®.
- Do not share REVLIMID® with other people.
- Do not take REVLIMID® if you are not enrolled in or do not meet the requirements of the RevAid® controlled distribution program.

REVLIMID® is not recommended for use in children under 18 years of age.

INTERACTIONS WITH THIS MEDICATION

Tell your healthcare provider about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. It is possible that REVLIMID® and other medicines may affect each other causing serious side effects.

Drugs that may interact with REVLIMID® include: digoxin, Hormonal Replacement Therapy, and Hormonal Contraception (estrogens and progestins).

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist.

PROPER USE OF THIS MEDICATION

Dosage: Myelodysplastic Syndrome: Starting dose: 10 mg daily on days 1-21 of 28-day cycles.

Your doctor may change the dosage during treatment, and will decide the total duration of therapy that you need. If you don't respond within 4 months of starting REVLIMID®, your doctor may decide to stop the treatment. It all depends on your response to the treatment.

Take REVLIMID® exactly as prescribed.

Swallow REVLIMID® capsules whole with water once a day. You should try to take it at about the same time each day.

Do not break, chew, or open your capsules.

It is important to remember that if you are being assisted with your medications, females who could become pregnant, or who plan to become pregnant can handle REVLIMID® capsules if they are using latex gloves.

You will have regular blood tests during your treatment with REVLIMID®. You should have your blood tested every week during your first 8 weeks of treatment, and at least monthly after that. Your healthcare provider may adjust your dose of REVLIMID® or interrupt your treatment based on the results of your blood tests and on your general condition.

Overdose:

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If less than 12 hours have passed since missing a dose, take the dose. If more than 12 hours have passed since missing a dose at the normal time, do not take the dose. Take the next dose at the normal time on the following day. Do **not** take 2 doses at the same time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, REVLIMID® can have side effects. The following are the most commonly reported side effects (≥ 10%):

Very Common: decrease in white blood cells, decrease in platelets, diarrhea, itchy skin, rash, tiredness, nausea, infection of the nasal passages, constipation, joint pain, back pain, swelling of arms and/or legs, fever, cough, dizziness, difficulty breathing, headache, decrease in red blood cells, muscle cramp, infection of the pharynx, upper respiratory tract infection, nose bleed, lack or loss of strength, dry skin, abdominal pain, pain in arm or leg, urinary tract infection, pneumonia, loss of appetite, decrease in blood potassium level, swelling, bronchitis, difficulty sleeping, sinus infection, vomiting, night sweats, muscle pain.

The following are commonly reported side effects (≥1% and <10%):

Common: fall, pain, increased sweating, bruise, upper abdominal pain, loose stools, arm and/or leg swelling, acquired decreased thyroid activity, high blood pressure, difficult or painful urination, dry mouth, toothache, allergy (rhinitis), flu, decreased sensitivity to stimulation, ruptured blood vessels, skin redness, chest pain, rigors, foot pain, distortion of sense of taste, loss of sensation in limbs, decrease in blood magnesium level, weight loss, infection under the skin, depression, skin lesion, flatulence, sensation of pricking, tingling, or creeping on the skin, heart palpitations, acute leukemia, hair loss, ear pain, dry eye, eye redness, eye pain.

Tell your doctor or pharmacist if you experience a side effect which is not listed above or any of the listed side effects that bother you or does not go away.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharma-cist
		Only if severe	In all cases	
Very common	Fever / Neutropenia (decrease in white blood cells)		√	
Very common	Bleeding from the gums or other sites or abnormal bleeding / Thrombocytopenia (decrease in platelets that help with blood clotting)		√	
Very common	Chest or other infections / Pneumonia, Sepsis, Flu, Various Infections		√	
Very common	Tiredness / Anemia (decrease in red blood cells), Fatigue, Acute Leukemia, Pancytopenia (decrease in platelet, red blood cell and white blood cell counts)		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very common	Difficulty breathing, breathlessness / Pulmonary Embolism (blood clot in or around the lungs), Heart failure, Pleural Effusion (excess fluid around the lungs), Hypoxia (decrease in oxygen to the body), Pneumonitis (inflammation of the lungs), Pulmonary Hypertension (increased blood pressure in vessels around or in the lungs), Pulmonary edema (build up of fluid in spaces outside blood vessels of the lungs)			√
Common	Nausea / Hyponatremia (decrease in sodium levels in the blood)		√	
Common	Skin rash		√	
Common	Muscle weakness / Asthenia (lack or loss of strength), Hypokalemia (decrease in potassium levels in blood)		√	
Common	Swelling of arms or legs / Edema peripheral, Kidney failure, Blood creatinine increase (decreased kidney function)			√
Common	Back pain	√		
Common	Loose or frequent bowel movements / Diarrhea	√		

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Arm or leg pain with swelling / Deep Vein Thrombosis (blood clots that form in your blood vessels)			√
Common	Dizziness or fainting	√		
Common	Headache / High blood pressure	√		
Common	Joint pain and muscle cramps	√		
Common	Heart palpitations, awareness of abnormal heart rhythm / Atrial fibrillation (abnormal or irregular heartbeats)			√
Common	Itchy skin	√		
Common	Pain	√		
Common	Chest pain / Angina		√	
Common	Vomiting	√		
Common	Difficulty moving limbs, walking or speaking / stroke and mini-stroke			√
Common	Confusion / Psychosomatic Disease (disorder having physical symptoms but originating from mental or emotional causes)		√	
Common	Dry mouth, excessive thirst, dark yellow urine / Dehydration		√	
Common	Difficulty swallowing / Dysphagia		√	
Common	Fall		√	
Common	Increased sweating		√	
Common	Loss of appetite / Anorexia		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / Effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharma-cist**
		Only if severe	**In all cases**	
Rare	Red rash across face and body / Peeling skin or blistered skin, flat red rash, fever, body aches (Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis)			√
Rare	Symptoms of tumor lysis syndrome: lack of urination, severe muscle weakness, heart rhythm disturbances, and seizures			√
Rare	Symptoms of tumor flare reaction: tender swollen lymph nodes, low-grade fever, pain, or rash			√
Rare	Symptoms of graft-versus-host disease following transplant (days/months): itchy and/or painful rash, diarrhea, abdominal pain, skin/eye yellowing		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / Effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharma-cist**
		Only if severe	**In all cases**	
Rare	Changes to blood thyroid hormone. Low thyroid hormone may cause fatigue, increased sensitivity to cold, constipation, dry skin, unexplained weight gain, puffy face, muscle weakness, slow heart rate, thinning hair, impaired memory. High thyroid hormone may cause anxiety or nervousness, weight loss, frequent and loose bowel movements, breathlessness, feeling hot and possibly feelings of having rapid, fluttering or pounding heart.			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Rare	Reactivation of viral infections including: herpes zoster (also known as 'shingles', a viral disease that causes a painful skin rash with blisters); hepatitis B that may cause symptoms of inflammation of the liver (hepatitis), itchy skin, jaundice (yellowing of the skin or whites of eyes), fever, tiredness, joint/muscle pain, loss of appetite, nausea and vomiting, pain in the upper right abdomen, pale stools and dark urine			√
Very Rare	Symptoms of muscle breakdown (rhabdomyolysis), muscle pain, weakness or swelling, dark urine		√	
Very Rare	Flu-like symptoms and a rash on the face then an extended rash with a high temperature and swollen glands (Drug reaction with eosinophilia and systemic symptoms [DRESS])			√

These are not all the possible side effects possible with the use of REVLIMID®. Ask your healthcare provider or pharmacist for more information.

HOW TO STORE IT

Store REVLIMID® at 15-30° C. Keep out of the reach of children. Contact RevAid® to return any unused REVLIMID® capsules.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

The information in this document is current as of the last revision date shown below. The most current information can be found at: www.RevAid.ca or by contacting the sponsor, Celgene, at:

1-888-RevAid1 (1-888-738-2431) or by visiting www.celgenecanada.net.

This leaflet was prepared by Celgene Inc.

Last revised: October 23, 2017

PrREVLIMID®

lenalidomide capsules

PART III: CONSUMER INFORMATION

MULTIPLE MYELOMA

This leaflet is part III of a three-part "Product Monograph" published when REVLIMID® (lenalidomide) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about REVLIMID®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

REVLIMID® can only be given to patients who are registered in and meet all conditions of the RevAid® program. RevAid® is a controlled distribution program of REVLIMID®.

What the medication is used for:

REVLIMID® is used with dexamethasone to treat patients with multiple myeloma who are not eligible for stem cell transplant. Multiple myeloma is a cancer of plasma cells. Plasma cells are found in the bone marrow. Plasma cells produce a protein called antibodies. Some antibodies can attack and kill disease causing germs. Patients with this type of cancer may have low blood cell counts and immune problems giving them a higher chance for getting infections such as pneumonia. The bones can be affected leading to bone pain and breaks (fractures).

What it does:

REVLIMID® works in multiple ways within the bone marrow to stop or slow the growth of cancerous myeloma cells.

When it should not be used:

Do not take REVLIMID® if:

- You are pregnant
- You are at risk of becoming pregnant
- You become pregnant during REVLIMID® treatment
- You are breastfeeding
- You are a male patient and are unable to follow or comply with the contraceptive measures of the RevAid Program
- **REVLIMID can cause an increased risk of death in people who have chronic lymphocytic leukemia (CLL).** Do not take REVLIMID® if you have CLL unless you are participating in a controlled clinical trial.
- You are allergic to lenalidomide, pomalidomide or thalidomide or any of the other ingredients in REVLIMID®. REVLIMID® contains lactose.

What the medicinal ingredient is:

lenalidomide

What the important nonmedicinal ingredients are:

Each capsule contains croscarmellose sodium, lactose anhydrous, magnesium stearate, and microcrystalline cellulose. The additional composition of the different capsule strengths is provided in the table below.

Strength	Imprint	Composition	Colour	Package size
2.5 mg	REV, 2.5 mg	FD&C blue #2, gelatin, titanium dioxide, yellow iron oxide	White opaque and blue/green opaque	21 count blisters
5 mg	REV, 5 mg	Gelatin, titanium dioxide	White opaque	28 count blisters
10 mg	REV, 10 mg	FD&C blue #2, gelatin, titanium dioxide, yellow iron oxide	Blue/green opaque and pale yellow opaque	28 count blisters
15 mg	REV, 15 mg	FD&C blue #2, gelatin, titanium dioxide	Powder blue opaque and white opaque	21 count blisters
20 mg	REV, 20 mg	FD&C blue #2, gelatin, titanium dioxide, yellow iron oxide	Blue-green opaque and powder blue opaque	21 count blisters
25 mg	REV, 25 mg	Gelatin, titanium dioxide	White opaque	21 count blisters

What dosage forms it comes in:

Capsules. Each capsule contains 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg or 25 mg of lenalidomide.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

REVLIMID® should only be prescribed by a doctor experienced in the use of anti-cancer drugs and registered with the RevAid® controlled distribution program.

Serious side effects may occur with the use of REVLIMID® and could include:

- birth defects (deformed babies) or death of an unborn baby and spontaneous abortion;
- decrease in the production of blood cells resulting in very low levels of white blood cells (neutropenia) and of platelets (thrombocytopenia);
- blood clots in the veins (Deep Vein Thrombosis), in the lung (Pulmonary Embolism), and in the arteries (heart attacks and stroke). Use of a blood thinner medication is recommended to reduce the risk;
- Liver problems. Treatment with REVLIMID® may lead to a higher risk of liver problems which may cause death.

REVLIMID® is only available under a controlled distribution program called RevAid®.

BEFORE you use REVLIMID® talk to your doctor or pharmacist if you:

- are pregnant or are planning to get pregnant
- are breastfeeding
- have kidney problems
- have liver problems
- have blood problems
- have or have had heart problems (irregular heart beat, heart attack)
- smoke, have high blood pressure or high cholesterol levels
- have had previous viral infection including herpes zoster infection (shingles) and/or hepatitis B virus infection (a viral infection of the liver)

REVLIMID® may cause birth defects. In order to take this drug you must meet the following conditions:

1. Females who can get pregnant:

- Discuss contraception (birth control) with your healthcare provider.
- Use at least two effective methods of contraception at the same time.
- Use these two effective methods of contraception:
  - For at least 4 weeks before starting REVLIMID® treatment
  - During interruptions of REVLIMID® treatment
  - During REVLIMID® treatment
  - For at least 4 weeks after stopping REVLIMID® treatment
- You must have two negative pregnancy tests before starting treatment:
  - The first 7-14 days prior to starting treatment
  - The second within 24 hours of starting treatment.
- You must have negative pregnancy tests during treatment:
  - Once weekly for the first 4 weeks
  - Once every 4 weeks (or once every 2 weeks if your period is irregular) for the duration of treatment and during treatment interruption

You must have a final pregnancy test 4 weeks after stopping REVLIMID®.

2. Males:

- REVLIMID® is present in the sperm of males who take this drug. Use a condom every time you have sexual intercourse with a woman who is pregnant or can get pregnant. This must be done even if you have undergone a successful vasectomy. The condom must be used while:
  - You are taking REVLIMID®
  - During interruptions of treatment
  - For 4 weeks after stopping REVLIMID®.
- Do not donate sperm while taking REVLIMID® and for 4 weeks after stopping REVLIMID®.
- Inform your sexual partner who can get pregnant that:
  - You are taking REVLIMID®
  - There is a risk of birth defects, stillbirths, and spontaneous abortions if a fetus is exposed to your sperm.
  - You must use a condom.

You should contact your doctor immediately if you think your female partner becomes pregnant while you are taking REVLIMID®.

3. All Patients:

REVLIMID® may cause birth defects and any method of birth control can fail. You should contact your doctor immediately if you think you or your female partner may be pregnant. You should also contact your doctor if you miss your period or experience unusual menstrual bleeding.

- Do not give blood while you take REVLIMID® and for 4 weeks after stopping REVLIMID®.

- Do not share REVLIMID® with other people.
- Do not take REVLIMID® if you are not enrolled in or do not meet the requirements of the RevAid® controlled distribution program.

REVLIMID® is not recommended for use in children under 18 years of age.

Second cancers such as skin cancers, blood cancers, and solid tumor cancers have been reported in a small number of patients while taking REVLIMID® or after treatment with REVLIMID® is completed. Patients should talk to their doctors if they have any concerns about their own increased risk of having other cancers.

INTERACTIONS WITH THIS MEDICATION

Tell your healthcare provider about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. It is possible that REVLIMID® and other medicines may affect each other causing serious side effects.

Drugs that may interact with REVLIMID® include: digoxin, Hormonal Replacement Therapy, and Hormonal Contraception (estrogens and progestins).

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist.

PROPER USE OF THIS MEDICATION

Dosage: Multiple Myeloma: Starting dose: 25 mg daily on days 1-21 of 28 day cycles in combination with dexamethasone.

Your doctor may change the dosage during treatment, and will continue therapy as long as you are responding to and tolerating REVLIMID®.

Take REVLIMID® exactly as prescribed.

Swallow REVLIMID® capsules whole with water once a day. You should try to take it at about the same time each day.

Do not break, chew, or open your capsules.

It is important to remember that if you are being assisted with your medication, females who could become pregnant, or who plan to become pregnant can handle REVLIMID® capsules if they are using latex gloves.

You will have regular blood tests during your treatment with REVLIMID®. You should have your blood tested once every week during the first 2 cycles (8 weeks) of treatment, every 2 weeks during the third cycle, and at least monthly after that. Your healthcare provider may adjust your dose of REVLIMID® or interrupt your treatment based on the results of your blood tests and on your general condition.

Overdose:

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If less than 12 hours have passed since missing a dose, take the dose. If more than 12 hours have passed since missing a dose at the normal time, do not take the dose. Take the next dose at the normal time on the following day. Do **not** take 2 doses at the same time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, REVLIMID® can have side effects. The following are the most commonly reported side effects (≥ 10%):

Very Common: chest and other infections, tiredness/lethargy, fever, muscle weakness, joint pain and muscle cramps, pain, abdominal pain, difficulty breathing/breathlessness, hard stools / difficult to pass, difficulty sleeping, diarrhea, bleeding from gums or other sites, numbness / abnormal sensations, dizziness, swelling of arms or legs, cough, cloudy (cataracts) or blurred vision, headache, nausea, skin rash, back pain, loss of appetite, weight loss, frequent hunger with excessive thirst and urination, taste altered, heart palpitations/awareness of abnormal heart rhythm, chest pain, swelling, mouth pain, general feeling of discomfort or uneasiness, sore throat, shaking, confusion, weight gain, depression, arm pain with arm or leg swelling, vomiting, reduced sense of touch, irritability, "pins and needles" in hands and feet, heartburn.

The following are commonly reported side effects (≥1% and <10%):

Common: bruise, increased sweating, dry skin, inflammation mouth, frequent urination, high blood pressure (headache), hoarse voice, dry mouth, stuffy nose, itchy skin, lightheadedness or dizziness, dehydration (dry mouth, excessive thirst, dark yellow urine), mood changes, hiccups, flatulence, runny nose, swelling face, sweating increased, skin redness, dizziness or fainting, muscle spasm, fever with shaking, face redness, balance impaired, canker sores, loose stools, bone pain, skin cancer, skin discoloration, decreased urination, hot flashes, painful urination, toothache, hair loss, increased tears, skin lesions, skin wound, decreased sex drive, nervousness, difficulty moving limbs, walking or speaking (stroke), dry eye, eye redness, fall, hives, memory impairment, difficulty swallowing, eye itch, rash, ringing in ears, allergic reaction, bedsores, blood in urine, deafness, increased hair growth, walking abnormally, increased appetite, mental status changes, non-coordinated muscle movement, painful or frequent urination, pale skin, urgent need to urinate, wheezing, wound.

Tell your doctor or pharmacist if you experience a side effect which is not listed above or any of the listed side effects that bother you or does not go away.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very common	Fever / Neutropenia (decrease in white blood cells)		√	
Very common	Muscle weakness / Asthenia (lack or loss of strength), Hypokalemia (decrease in potassium levels in blood), Hypophosphatemia (decrease in phosphate levels in blood)		√	
Very common	Tiredness / Anemia (decrease in red blood cells), Fatigue		√	
Very common	Bleeding from the gums or other sites or abnormal bleeding / Thrombocytopenia (decrease in platelets that help with blood clotting)		√	
Very common	Chest or other infections / Pneumonia, Various Infections		√	
Very common	Arm or leg pain with swelling / Deep Vein Thrombosis (blood clots that form in your blood vessels)			√
Very common	"Pins and needles" in hands and feet / Hypocalcaemia (low blood calcium)		√	
Common	Frequent hunger, excessive thirst or urination / Hyperglycemia (high blood sugar)			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Difficulty breathing, breathlessness / Pulmonary Embolism (blood clot in or around the lungs) / Heart Failure / Pulmonary edema			√
Common	Lightheadedness, dizziness or fainting / Hypotension (low blood pressure)	√		
Common	Heart palpitations, awareness of abnormal heart rhythm / Atrial fibrillation (abnormal or irregular heartbeats)			√
Common	Loose or frequent bowel movements / Diarrhea	√		
Common	Depression		√	
Common	Bone Pain	√		
Common	Confusion		√	
Common	Constipation	√		
Common	Numbness, abnormal sensations / Neuropathy (a disease of the nerves)		√	
Common	Nausea		√	
Common	Headache / High blood pressure	√		
Common	Dry mouth, excessive thirst, dark yellow urine / Dehydration		√	
Common	Rapid swelling of the skin, face and lips / Angioedema			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Chest pain spreading to arms, neck, jaw, back or stomach, feeling sweaty and breathless, feeling sick or vomiting which may be symptoms of a heart attack			√
Common	Production of much more or much less urine than usual which may be symptoms of kidney failure			√
Common	Shortness of breath especially when lying down which may be a symptom of heart failure			√
Rare	Red rash across face and body / Peeling skin or blistered skin, flat red rash, fever, body aches (Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis)			√
Rare	Symptoms of tumor lysis syndrome: lack of urination, severe muscle weakness, heart rhythm disturbances, and seizures			√
Rare	Symptoms of tumor flare reaction: tender swollen lymph nodes, low-grade fever, pain, or rash			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Rare	Symptoms of graft-versus-host disease following transplant (days/months): itchy and/or painful rash, diarrhea, abdominal pain, skin/eye yellowing		√	
Rare	Changes to blood thyroid hormone. Low thyroid hormone may cause fatigue, increased sensitivity to cold, constipation, dry skin, unexplained weight gain, puffy face, muscle weakness, slow heart rate, thinning hair, impaired memory. High thyroid hormone may cause anxiety or nervousness, weight loss, frequent and loose bowel movements, breathlessness, feeling hot and possibly feelings of having rapid, fluttering or pounding heart.			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharma-cist
		Only if severe	In all cases	
Very Rare	Reactivation of viral infections: including herpes zoster (also known as 'shingles', a viral disease that causes a painful skin rash with blisters); hepatitis B which may cause symptoms of inflammation of the liver (hepatitis), itchy skin, jaundice (yellowing of the skin or whites of eyes), fever, tiredness, joint/muscle pain, loss of appetite, nausea and vomiting, pain in the upper right abdomen, pale stools and dark urine			√
Very Rare	Symptoms of muscle breakdown (rhabdomyolysis), muscle pain, weakness or swelling, dark urine		√	
Very Rare	Flu-like symptoms and a rash on the face then an extended rash with a high temperature and swollen glands (Drug reaction with eosinophilia and systemic symptoms [DRESS])			√

These are not all the possible side effects possible with the use of REVLIMID®. Ask your healthcare provider or pharmacist for more information.

HOW TO STORE IT

Store REVLIMID® at 15-30° C. Keep out of the reach of children. Contact RevAid® to return any unused REVLIMID® capsules.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect

- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

The information in this document is current as of the last revision date shown below. The most current information can be found at: www.RevAid.ca or by contacting the sponsor, Celgene, at:

1-888-RevAid1 (1-888-738-2431) or visiting www.celgenecanada.net.

This leaflet was prepared by Celgene Inc.

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