REVLIMID® (lenalidomide)

5 mg, 10 mg, 15 mg and 25 mg capsules

WARNINGS:

1. **POTENTIAL FOR HUMAN BIRTH DEFECTS**
2. **HEMATOLOGIC TOXICITY (NEUTROPENIA AND THROMBOCYTOPENIA)**
3. **DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM**

POTENTIAL FOR HUMAN BIRTH DEFECTS

WARNING: POTENTIAL FOR HUMAN BIRTH DEFECTS

LENALIDOMIDE IS AN ANALOGUE OF THALIDOMIDE. THALIDOMIDE IS A KNOWN HUMAN TERATOGEN THAT CAUSES SEVERE LIFE-THREATENING HUMAN BIRTH DEFECTS. IF LENALIDOMIDE IS TAKEN DURING PREGNANCY, IT MAY CAUSE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY. FEMALES SHOULD BE ADVISED TO AVOID PREGNANCY WHILE TAKING REVLIMID® (lenalidomide).

Special Prescribing Requirements

BECAUSE OF THIS POTENTIAL TOXICITY AND TO AVOID FETAL EXPOSURE TO REVLIMID® (lenalidomide), REVLIMID® (lenalidomide) IS ONLY AVAILABLE UNDER A SPECIAL RESTRICTED DISTRIBUTION PROGRAM. THIS PROGRAM IS CALLED "RevAssist®." UNDER THIS PROGRAM, ONLY PRESCRIBERS AND PHARMACISTS REGISTERED WITH THE PROGRAM CAN PRESCRIBE AND DISPENSE THE PRODUCT. IN ADDITION, REVLIMID® (lenalidomide) MUST ONLY BE DISPENSED TO PATIENTS WHO ARE REGISTERED AND MEET ALL THE CONDITIONS OF THE RevAssist® PROGRAM.

PLEASE SEE THE FOLLOWING INFORMATION FOR PRESCRIBERS, FEMALE PATIENTS, AND MALE PATIENTS ABOUT THIS RESTRICTED DISTRIBUTION PROGRAM.

RevAssist® PROGRAM DESCRIPTION

Prescribers

REVLIMID® (lenalidomide) can be prescribed only by licensed prescribers who are registered in the RevAssist® program and understand the potential risk of teratogenicity if lenalidomide is used during pregnancy.

Effective contraception must be used by female patients of childbearing potential for at least 4 weeks before beginning REVLIMID® (lenalidomide) therapy, during REVLIMID® (lenalidomide) therapy, during dose interruptions and for 4 weeks following discontinuation of REVLIMID® (lenalidomide) therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or because the patient has been postmenopausal naturally for at least 24 consecutive months. Two reliable forms of contraception must be used simultaneously unless continuous abstinence from heterosexual sexual contact is the chosen method. Females of childbearing potential should be referred to a qualified provider of contraceptive methods, if needed. Sexually mature females who have not undergone a hysterectomy, have not had a bilateral oophorectomy or who have not been postmenopausal naturally for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months) are considered to be females of childbearing potential.

Before prescribing REVLIMID® (lenalidomide), females of childbearing potential should have 2 negative pregnancy tests (sensitivity of at least 50 mIU/mL). The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing REVLIMID® (lenalidomide). A prescription for REVLIMID® (lenalidomide) for a female of childbearing potential must not be issued by the prescriber until negative pregnancy tests have been verified by the prescriber.

Male Patients: It is not known whether lenalidomide is present in the semen of patients receiving the drug. Therefore, males receiving REVLIMID® (lenalidomide) must always use a latex condom during any sexual contact with females of childbearing potential even if they have undergone a successful vasectomy.

Once treatment has started and during dose interruptions, pregnancy testing for females of childbearing potential should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her pregnancy test or in her menstrual bleeding. REVLIMID® (lenalidomide) treatment must be discontinued during this evaluation.

Pregnancy test results should be verified by the prescriber and the pharmacist prior to dispensing any prescription.

If pregnancy does occur during REVLIMID® (lenalidomide) treatment, REVLIMID® (lenalidomide) must be discontinued immediately.

Any suspected fetal exposure to REVLIMID® (lenalidomide) should be reported to the FDA via the MedWatch number at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Female Patients

REVLIMID® (lenalidomide) should be used in females of childbearing potential only when the patient MEETS ALL OF THE FOLLOWING CONDITIONS (i.e., she is unable to become pregnant while on lenalidomide therapy):

- she understands and can reliably carry out instructions.
- she is capable of complying with the mandatory contraceptive measures, pregnancy testing, patient registration, and patient survey as described in the RevAssist® program.
- she has received and understands both oral and written warnings of the potential risks of taking lenalidomide during pregnancy and of exposing a fetus to the drug.
- she has received both oral and written warnings of the risk of possible contraception failure and of the need to use two reliable forms of contraception simultaneously, unless continuous abstinence from heterosexual sexual contact is the chosen method. Sexually mature females who have not undergone a hysterectomy or who have not been postmenopausal for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months), or had a bilateral oophorectomy are considered to be females of childbearing potential.
- she acknowledges, in writing, her understanding of these warnings and of the need for using two reliable methods of contraception for 4 weeks prior to beginning lenalidomide therapy, during lenalidomide therapy, during dose interruptions and for 4 weeks after discontinuation of lenalidomide therapy.
- she has had two negative pregnancy tests with a sensitivity of at least 50 mIU/mL, within 10-14 days and 24 hours prior to beginning therapy.
- if the patient is between 12 and 18 years of age, her parent or legal guardian must have read the educational materials and agreed to ensure compliance with the above.

Male Patients

REVLIMID® (lenalidomide) should be used in sexually active males when the PATIENT MEETS ALL OF THE FOLLOWING CONDITIONS:

- he understands and can reliably carry out instructions.
- he is capable of complying with the mandatory contraceptive measures that are appropriate for men, patient registration, and patient survey as described in the RevAssist® program.
- he has received and understands both oral and written warnings of the potential risks of taking lenalidomide and exposing a fetus to the drug.

- he has received both oral and written warnings of the risk of possible contraception failure and that it is unknown whether lenalidomide is present in semen. He has been instructed that he must always use a latex condom during any sexual contact with females of childbearing potential, even if he has undergone a successful vasectomy.

- he acknowledges, in writing, his understanding of these warnings and of the need to use a latex condom during any sexual contact with females of childbearing potential, even if he has undergone a successful vasectomy. Females of childbearing potential are considered to be sexually mature females who have not undergone a hysterectomy, have not had a bilateral oophorectomy or who have not been postmenopausal for at least 24 consecutive months (i.e., who have had menses at any time in the preceding 24 consecutive months).

- if the patient is between 12 and 18 years of age, his parent or legal guardian must have read the educational materials and agreed to ensure compliance with the above.

HEMATOLOGIC TOXICITY (NEUTROPENIA AND THROMBOCYTOPENIA)

This drug is associated with significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q myelodysplastic syndromes had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q myelodysplastic syndromes should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors. (See DOSAGE AND ADMINISTRATION)

DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM

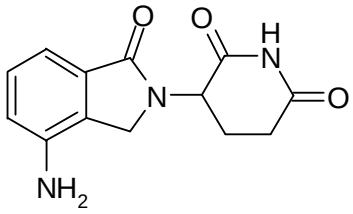
This drug has demonstrated a significantly increased risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients with multiple myeloma who were treated with REVLIMID® (lenalidomide) combination therapy. Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with REVLIMID® (lenalidomide) may lessen the potential for venous thromboembolic events. The decision to take prophylactic measures should be done carefully after an assessment of an individual patient's underlying risk factors.

You can get the information about REVLIMID® (lenalidomide) and the RevAssist® program on the internet at www.REVLIMID.com or by calling the manufacturer's toll free number 1-888-423-5436.

DESCRIPTION

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

Chemical Structure of Lenalidomide



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

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

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

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

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses antineoplastic, immunomodulatory and antiangiogenic properties. Lenalidomide inhibited the secretion of pro-inflammatory cytokines and increased the secretion of antiinflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibited cell proliferation with varying effectiveness (IC50s) in some but not all cell lines. Of cell lines tested, lenalidomide was effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5) but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions. Lenalidomide inhibited the growth of multiple

myeloma cells from patients, as well as MM.1S cells (a human multiple myeloma cell line), by inducing cell cycle arrest and apoptosis.

Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 in vitro.

Pharmacokinetics and Drug Metabolism

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.

Pharmacokinetic sampling in myelodysplastic syndromes (MDS) patients was not performed. In multiple myeloma 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 is 57% higher than in healthy male volunteers.

Pharmacokinetic Parameters

Distribution:

In vitro (^{14}C)-lenalidomide binding to plasma proteins is approximately 30%.

Metabolism and Excretion:

The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.

Special Populations:

Patients with 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 (creatinine clearance 57-74 mL/min), 6 patients with moderate renal function impairment (creatinine clearance 33-46 mL/min), 6 patients with severe renal function impairment (creatinine clearance 17-29 mL/min), and 6 patients with end stage renal disease requiring dialysis were administered a single oral 25-mg dose of REVLIMID® (lenalidomide). As a control group comparator, 7 healthy subjects of similar age with normal renal function (creatinine clearance 83-145 mL/min) were also administered a single oral 25-mg dose of REVLIMID® (lenalidomide). As creatinine

clearance decreased from mild to severe impairment, half-life increased and drug clearance decreased linearly. Patients with moderate and severe renal impairment had a 3-fold increase in half-life and a 66% to 75% decrease in drug clearance compared to healthy subjects. Patients on hemodialysis (n=6) given a single, 25-mg dose of lenalidomide had an approximate 4.5-fold increase in half-life and an 80% decrease in drug clearance compared to healthy subjects. Approximately 40% of the administered dose was removed from the body during a single dialysis session.

Adjustment of the starting dose of REVLIMID® (lenalidomide) is recommended in patients with moderate or severe renal impairment and in patients on dialysis. See **DOSAGE AND ADMINISTRATION.**

In multiple myeloma patients, those patients with mild renal impairment had an AUC 56% greater than those with normal renal function.

Patients with Hepatic Disease: The pharmacokinetics of lenalidomide in patients with hepatic impairment have not been studied.

Age: The effects of age on the pharmacokinetics of lenalidomide have not been studied.

Pediatric: No pharmacokinetic data are available in patients below the age of 18 years.

Gender: The effects of gender on the pharmacokinetics of lenalidomide have not been studied.

Race: Pharmacokinetic differences due to race have not been studied.

CLINICAL STUDIES

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

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

This major study enrolled 148 patients who had RBC transfusion dependent anemia. RBC-transfusion dependence was defined as having received $\geq$ 2 units of RBCs within 8 weeks prior to study treatment. The study enrolled patients with absolute neutrophil counts (ANC) $\geq 500/mm^3$, platelet counts $\geq 50{,}000/mm^3$, serum creatinine $\leq$ 2.5 mg/dL, serum SGOT/AST or SGPT/ALT $\leq$ 3.0 x upper limit of normal (ULN), and serum direct bilirubin $\leq$ 2.0 mg/dL. Granulocyte colony-stimulating factor was permitted for patients who developed neutropenia or fever in association with neutropenia. Baseline patient and disease-related characteristics are summarized in Table 1.

Table 1: Baseline Demographic and Disease-Related Characteristics

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

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

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

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

Ninety percent of patients who achieved a transfusion benefit did so by completion of three months in the study.

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

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

reduction or interruption was 51 days (mean, 59.7 days; range, 15-205 days) and the median duration of the second dose interruption was 21 days (mean, 26 days; range, 2-148 days).

Granulocyte colony-stimulating factors were permitted for patients who developed neutropenia or fever in association with neutropenia.

Multiple Myeloma

Two randomized studies (Studies 1 and 2) were conducted to evaluate the efficacy and safety of REVLIMID® (lenalidomide). These multicenter, multinational, double-blind, placebo-controlled studies compared REVLIMID® (lenalidomide) plus oral pulse high-dose dexamethasone therapy to dexamethasone therapy alone, in patients with multiple myeloma who had received at least one prior treatment.

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

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

In both studies, dose adjustments were allowed based on clinical and laboratory findings. Sequential dose reductions to 15 mg daily, 10 mg daily and 5 mg daily were allowed for toxicity. (See **DOSAGE AND ADMINISTRATION**)

Table 2 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® (lenalidomide)/dexamethasone and placebo/dexamethasone groups.

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299 **Table 2: Baseline Demographic and Disease-Related Characteristics –**
300 **Studies 1 and 2**

	Study 1		Study 2	
	REVLIMID/Dex N=170	**Placebo/Dex N=171**	**REVLIMID/Dex N=176**	**Placebo/Dex N=175**
Patient Characteristics				
Age (years) Median Min, Max	 64 36, 86	 62 37, 85	 63 33, 84	 64 40, 82
Sex Male Female	 102 (60%) 68 (40%)	 101 (59%) 70 (41%)	 104 (59%) 72 (41%)	 103 (59%) 72 (41%)
Race/Ethnicity White Other	 134 (79%) 36 (21%)	 143 (84%) 28 (16%)	 172 (98%) 4 (2%)	 175(100%) 0 (0%)
ECOG Performance Status 0-1	151 (89%)	163 (95%)	150 (85%)	144 (82%)
Disease Characteristics				
Baseline Multiple Myeloma Stage (Durie-Salmon) I II III	 2% 31% 67%	 2% 31% 67%	 6% 28% 65%	 5% 33% 63%
Baseline Creatinine (mg/dL) Median Min, Max	 1.0 0.4, 2.6	 1.0 0.5, 2.4	 0.9 0.3, 2.3	 0.9 0.5, 2.3
B2-microglobulin (mg/L) Median Min, Max	 3.7 1.1, 45	 3.3 1.3, 15.2	 3.4 1.0, 14.4	 3.3 1.3, 25.3
Number of Prior Therapies				
No. of Prior Antimyeloma Therapies 1 ≥ 2	 38% 62%	 37% 63%	 32% 68%	 33% 67%
Types of Prior Therapies				
Stem Cell Transplantation	60%	60%	56%	54%
Thalidomide	42%	46%	30%	38%
Dexamethasone	80%	70%	66%	69%
Bortezomib	11%	12%	5%	4%
Melphalan	34%	31%	56%	52%
Doxorubicin	55%	52%	56%	57%

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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.

Preplanned interim analyses of both studies showed that the combination of REVLIMID® (lenalidomide)/dexamethasone was significantly superior to dexamethasone alone for TTP. The studies were unblinded to allow patients in the placebo/dexamethasone group to receive treatment with the REVLIMID® (lenalidomide)/dexamethasone combination.

Table 3 summarizes TTP and response rates based on the best response assessments for Studies 1 and 2.

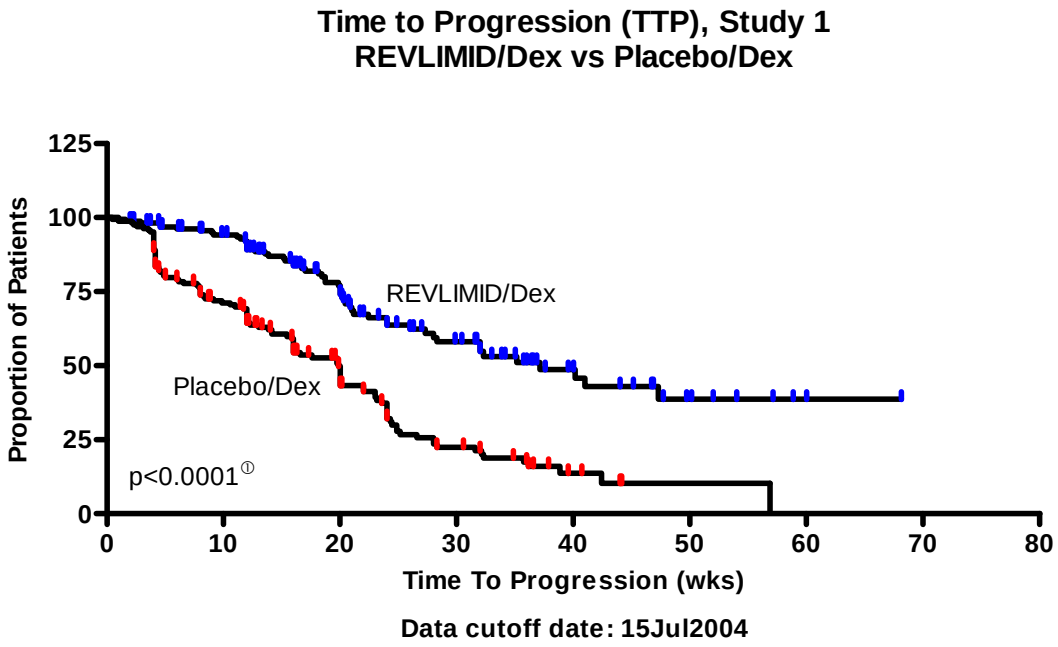
Table 3: Summary of Efficacy Analysis — Studies 1 and 2

	Study 1		Study 2	
	REVLIMID/Dex N=170	**Placebo/Dex N=171**	**REVLIMID/Dex N=176**	**Placebo/Dex N=175**
TTP				
Censored n (%)	115 (68)	61 (36)	133 (76)	78 (45)
Median TTP in weeks [95% CI]	37.1 [28, NE[1]]	19.9 [16, 22]	NE[1]	20 [19.9, 21.6]
Hazard Ratio[2] [95% CI]	0.356 [0.257, 0.494]		0.392 [0.274, 0.562]	
Log-rank Test p-value [3]	<0.0001		<0.0001	
Response				
Complete Response (CR) n (%)	14 (8)	1 (1)	14 (8)	1 (1)
Partial Response (RR/PR) n (%)	76 (44)	27 (16)	76 (43)	33 (19)
Overall Response n (%)	90 (53)	28 (16)	90 (51)	34 (19)
p-value	<0.0001		<0.0001	
Odds Ratio [95% CI]	5.5 [3.3, 9.1]		4.3 [2.7, 7.0]	

[1] NE, Not estimable due to short follow-up.
[2] Hazard Ratio of Revlimid/Dexamethasone to Placebo/Dexamethasone
[3] The p-value is based on a one-tailed unstratified log rank test.

Figures 1 and 2 depict the Kaplan-Meier estimates of TTP in Studies 1 and 2, respectively.

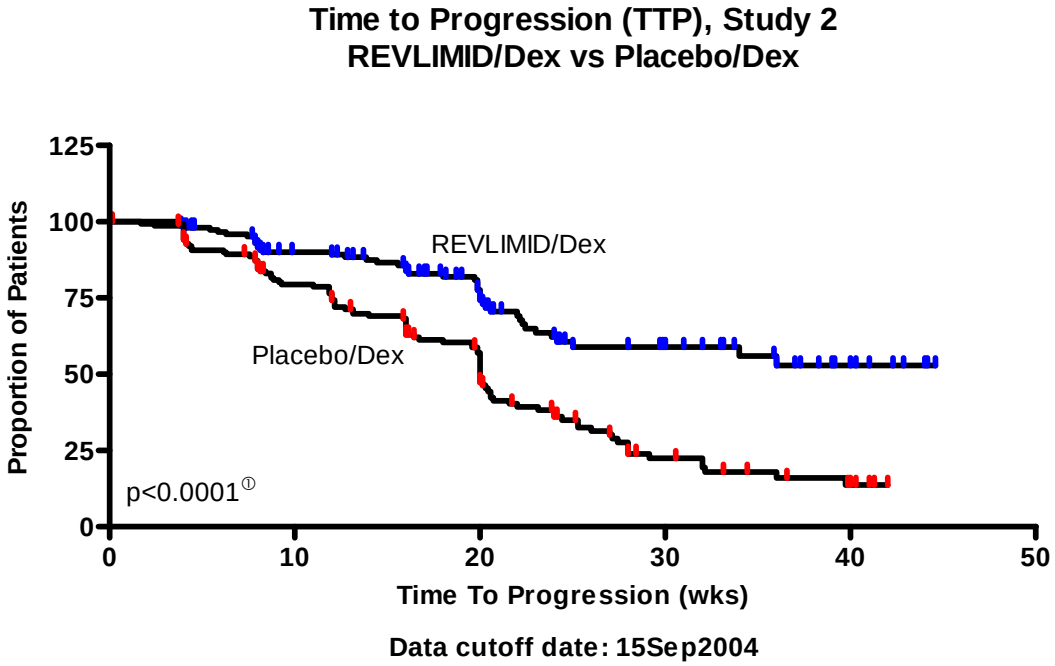
Figure 1: Kaplan-Meier Estimate of Time to Progression — Study 1



① p-value from log-rank test

The median duration of Study 1 follow-up was 20.1 weeks.

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



① p-value from log-rank test

The median duration of Study 2 follow-up was 22.3 weeks.

INDICATIONS AND USAGE

REVLIMID® (lenalidomide) is indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

REVLIMID® (lenalidomide) in combination with dexamethasone is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy.

CONTRAINDICATIONS

Pregnancy Category X: (See BOXED WARNINGS)

Due to its structural similarities to thalidomide, a known human teratogen, and data from an embryofetal development study showing treatment with lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy, lenalidomide is contraindicated in pregnant women and women capable of becoming pregnant. (See **BOXED WARNINGS**.) When there is no alternative, females of childbearing potential may be treated with lenalidomide provided adequate precautions are taken to avoid pregnancy. Females must commit either to abstain continuously from

heterosexual sexual intercourse or to use two methods of reliable birth control, including at least one highly effective method (e.g., IUD, hormonal contraception, tubal ligation, or partner's vasectomy) and one additional effective method (e.g., latex condom, diaphragm, or cervical cap), beginning 4 weeks prior to initiating treatment with REVLIMID® (lenalidomide), during therapy with REVLIMID® (lenalidomide), during therapy delay, and continuing for 4 weeks following discontinuation of REVLIMID® (lenalidomide) therapy. If hormonal or IUD contraception is medically contraindicated, two other effective or highly effective methods may be used.

Females of childbearing potential being treated with REVLIMID® (lenalidomide) should have pregnancy testing (sensitivity of at least 50 mIU/mL). The first test should be performed within 10-14 days and the second test within 24 hours prior to beginning REVLIMID® (lenalidomide) therapy and then weekly during the first month of REVLIMID® (lenalidomide), then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding. If pregnancy occurs, REVLIMID® (lenalidomide) must be immediately discontinued. Under these conditions, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

REVLIMID® (lenalidomide) is contraindicated in any patients who have demonstrated hypersensitivity to the drug or its components.

WARNINGS

Pregnancy Category X: (See BOXED WARNINGS and CONTRAINDICATIONS)

REVLIMID® (lenalidomide) is an analogue of thalidomide. Thalidomide is a known human teratogen that causes life-threatening human birth defects. An embryofetal development study in non-human primates indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy, similar to birth defects observed in humans following exposure to thalidomide during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. REVLIMID® (lenalidomide) may cause fetal harm when administered to a pregnant female. Females of childbearing potential should be advised to avoid pregnancy while on REVLIMID® (lenalidomide). Two effective contraceptive methods should be used during therapy, during therapy interruptions and for at least 4 weeks after completing therapy.

There are no adequate and well-controlled studies in pregnant females.

Because of this potential toxicity and to avoid fetal exposure to REVLIMID® (lenalidomide), REVLIMID® (lenalidomide) is only available under a special restricted distribution program. This program is called RevAssist®.

Lenalidomide has been shown to have an embryocidal effect in rabbits at a dose of 50 mg/kg (approximately 120 times the human dose of 10 mg based on body surface area).

An embryo-fetal development study in rats revealed no teratogenic effects at the highest dose of 500 mg/kg (approximately 600 times the human dose of 10 mg based on body surface area). At 100, 300 or 500 mg/kg/day there was minimal maternal toxicity that included slight, transient, reduction in mean body weight gain and food intake. However this animal model may not adequately address the full spectrum of the potential embryo-fetal developmental effects of lenalidomide.

A pre- and post-natal development study in rats revealed few adverse effects on the offspring of female rats treated with lenalidomide at doses up to 500 mg/kg (approximately 600 times the human dose of 10 mg based on body surface area). The male offspring exhibited slightly delayed sexual maturation and the female offspring had slightly lower body weight gains during gestation when bred to male offspring.

The structural similarity of lenalidomide to thalidomide, a known human teratogen, as well as malformations seen in the offspring of female monkeys administered lenalidomide during pregnancy, suggests a potential risk to the developing fetus.

HEMATOLOGIC TOXICITY (NEUTROPENIA AND THROMBOCYTOPENIA):

This drug is associated with significant neutropenia and thrombocytopenia.

Eighty percent of patients with del 5q MDS had to have a dose delay or reduction during the major study for the indication. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. In the 48% of patients who developed Grade 3 or 4 neutropenia, the median time to onset was 42 days (range, 14-411 days), and the median time to documented recovery was 17 days (range, 2-170 days). In the 54% of patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was 28 days (range, 8-290 days), and the median time to documented recovery was 22 days (range, 5-224 days). Patients on therapy for del 5q myelodysplastic syndromes should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors. (See DOSAGE AND ADMINISTRATION)

In the pooled multiple myeloma studies Grade 3 and 4 hematologic toxicities were more frequent in patients treated with the combination of REVLIMID® (lenalidomide) and dexamethasone than in patients treated with dexamethasone alone. (See ADVERSE REACTIONS: Table 7.) Patients on therapy should have their complete blood counts monitored every 2 weeks for the first 12 weeks and then monthly thereafter. Patients may require dose interruption and/or dose reduction. (See DOSAGE AND ADMINISTRATION)

DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM:

This drug has demonstrated a significantly increased risk of DVT and PE in patients with multiple myeloma who were treated with REVLIMID® (lenalidomide)

combination therapy. Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with REVLIMID® (lenalidomide) may lessen the potential for venous thromboembolic events. The decision to take prophylactic measures should be done carefully after an assessment of an individual patient's underlying risk factors. (See ADVERSE REACTIONS: Table 7)

PRECAUTIONS

Angioedema, Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive REVLIMID®. REVLIMID® interruption or discontinuation should be considered for Grade 2-3 skin rash. REVLIMID® must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions.

Tumor Lysis Syndrome

Lenalidomide has antineoplastic activity and therefore the complications of tumor lysis syndrome may occur. The patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Information for Patients

Patients should be counseled on lenalidomide's potential risk of teratogenicity due to its structural similarity to thalidomide and data from an embryofetal development study showing treatment with lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. Patients may only acquire a prescription for REVLIMID® (lenalidomide) therapy through a controlled distribution program (RevAssist®) through contracted pharmacies. Female patients of childbearing potential will be educated and counseled on the requirements of the RevAssist® program and the precautions to be taken to preclude fetal exposure to REVLIMID® (lenalidomide). Patients should become familiar with the REVLIMID® (lenalidomide) RevAssist® educational materials and Patient Medication Guide, and direct any questions to their physician or pharmacist prior to starting REVLIMID® (lenalidomide) therapy.

Laboratory Tests

The MDS clinical study enrolled patients with absolute neutrophil counts (ANC) ≥ 500/mm^3, platelet counts ≥ 50,000/mm^3, serum creatinine ≤ 2.5 mg/dL, serum SGOT/AST or SGPT/ALT ≤ 3.0 x upper limit of normal (ULN), and serum direct bilirubin ≤ 2.0 mg/dL**.** A complete blood cell count (CBC), including white blood cell count with differential, platelet count, hemoglobin, and hematocrit should be performed weekly for the first 8 weeks of REVLIMID® (lenalidomide) treatment and monthly thereafter to monitor for cytopenias.

The multiple myeloma Studies 1 and 2 enrolled patients with absolute neutrophil counts (ANC) ≥ 1000 /mm^3, platelet counts ≥ 75,000/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. A CBC should be performed every two weeks for the first three months and at least monthly thereafter to monitor for cytopenias.

Drug Interactions

Results from human in vitro metabolism studies and nonclinical studies show that REVLIMID® (lenalidomide) is neither metabolized by nor inhibits or induces the cytochrome P450 pathway suggesting that lenalidomide is not likely to cause or be subject to P450-based metabolic drug interactions in man.

Co-administration of multiple doses of 10 mg of lenalidomide had no effect on the single dose pharmacokinetics of R- and S-warfarin. Co-administration of single 25-mg dose 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 lenalidomide administration.

When digoxin was co-administered with lenalidomide 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 lenalidomide.

Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenicity: Carcinogenicity studies with lenalidomide have not been conducted.

Mutagenesis: 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.

Fertility: A fertility and early embryonic development study in rats, with administration of lenalidomide up to 500 mg/kg (approximately 600 times the human dose of 10 mg, based on body surface area) produced no parental toxicity and no adverse effects on fertility.

Pregnancy

Pregnancy Category X: (See BOXED WARNINGS and CONTRAINDICATIONS)

Because of the structural similarity to thalidomide, a known human teratogen, and the data from an embryofetal development study showing treatment with lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy, REVLIMID® (lenalidomide) is contraindicated in females who are or may become pregnant and who are not using the two required types of birth control or who are not continually abstaining from reproductive heterosexual sexual intercourse. REVLIMID® (lenalidomide) should not be used by females who are pregnant or who could become pregnant while taking the drug. If pregnancy does occur during treatment, the drug should be immediately discontinued. Under these conditions, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure to REVLIMID® (lenalidomide) should be reported to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.

Use in Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from lenalidomide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 have not been established.

Geriatric Use

REVLIMID® (lenalidomide) has been used in del 5q MDS clinical trials in patients up to 95 years of age.

Of the 148 patients with del 5q MDS enrolled in the major study, 38% were age 65 and over, while 33% were age 75 and over. Although the overall frequency of adverse events (100%) was the same in patients over 65 years of age as in younger patients, the frequency of serious adverse events was higher in patients over 65 years of age than in younger patients (54% vs. 33%). A greater proportion of patients over 65 years of age discontinued from the clinical studies because of adverse events than the proportion of younger patients (27% vs.16%). No differences in efficacy were observed between patients over 65 years of age and younger patients.

REVLIMID® (lenalidomide) has been used in multiple myeloma (MM) clinical trials in patients up to 86 years of age.

Of the 692 MM patients enrolled in Studies 1 and 2, 45% were age 65 or over while 12% of patients were age 75 and over. The percentage of patients age 65 or over was not significantly different between the REVLIMID® (lenalidomide)/dexamethasone and placebo/dexamethasone groups. Of the 346 patients who received REVLIMID® (lenalidomide)/dexamethasone, 46% were age 65 and over. In both studies, patients > 65 years of age were more likely than patients ≤ 65 years of age to experience diarrhea, fatigue, pulmonary embolism, and syncope following use of REVLIMID® (lenalidomide). No differences in efficacy were observed between patients over 65 years of age and younger patients.

Renal Impairment

Since lenalidomide is primarily excreted unchanged by the kidney, adjustments to the starting dose of REVLIMID® (lenalidomide) are recommended to provide appropriate drug exposure in patients with moderate or severe renal impairment and in patients on dialysis. See **DOSAGE AND AMINISTRATION**.

ADVERSE REACTIONS

Myelodysplastic Syndromes

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

Thrombocytopenia (61.5%; 91/148) and neutropenia (58.8%; 87/148) were the most frequently reported adverse events observed. The next most common adverse events observed were diarrhea (48.6%; 72/148), pruritus (41.9%; 62/148), rash (35.8%; 53/148) and fatigue (31.1%; 46/148). Table 4 summarizes the adverse events that were reported in ≥ 5% of the REVLIMID® (lenalidomide) treated patients in the del 5q MDS clinical study. Table 5 summarizes the most frequently observed Grade 3 and Grade 4 adverse reactions regardless of relationship to treatment with REVLIMID® (lenalidomide). In the single-arm studies conducted, it is often not possible to distinguish adverse events that are drug-related and those that reflect the patient's underlying disease.

Table 4: Summary of Adverse Events Reported in ≥5% of the REVLIMID® (lenalidomide) Treated Patients in del 5q MDS Clinical Study

System organ class/Preferred term [a]	10 mg Overall (N=148)	
Patients with at least one adverse event	148	(100.0)
Blood and Lymphatic System Disorders		
Thrombocytopenia	91	(61.5)
Neutropenia	87	(58.8)
Anemia NOS	17	(11.5)

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

Insomnia	15	(10.1)
Depression	8	(5.4)
Vascular Disorders		
Hypertension NOS	9	(6.1)
Renal and Urinary Disorders		
Dysuria	10	(6.8)
Cardiac Disorders		
Palpitations	8	(5.4)
Endocrine Disorders		
Acquired Hypothyroidism	10	(6.8)

NOS, not otherwise specified

[a] 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 patient with multiple occurrences of an AE is counted only once in the AE category.

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Table 5: Most Frequently Observed Grade 3 and 4 Adverse Events [1] Regardless of Relationship to Study Drug Treatment

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

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

[2] 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 other clinical studies of REVLIMID® (lenalidomide) in MDS patients, the following serious adverse events (regardless of relationship to study drug treatment) not described in Table 4 or 5 were reported:

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

Cardiac disorders: cardiac failure congestive, atrial fibrillation, angina pectoris, cardiac arrest, cardiac failure NOS, cardio-respiratory arrest, cardiomyopathy NOS, myocardial

infarction, myocardial ischemia, atrial fibrillation aggravated, bradycardia NOS, cardiogenic shock, pulmonary edema NOS, supraventricular arrhythmia NOS, tachyarrhythmia, ventricular dysfunction

Ear and labyrinth disorders: vertigo

Endocrine disorders: Basedow's disease

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

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

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

Immune system disorders: hypersensitivity NOS

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

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

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

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

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

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

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

Psychiatric disorders: confusional state

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

Reproductive system and breast disorders: pelvic pain NOS

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

Skin and subcutaneous tissue disorders: acute febrile neutrophilic dermatosis

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

Multiple Myeloma

Data were evaluated from 691 patients in two studies who received at least one dose of REVLIMID® (lenalidomide)/dexamethasone (346 patients) or placebo/dexamethasone (345 patients).

In the REVLIMID® (lenalidomide)/dexamethasone treatment group, 151 patients (45%) underwent at least one dose interruption with or without a dose reduction of REVLIMID® (lenalidomide) compared to 21% in the placebo/dexamethasone treatment group. Of these patients who had one dose interruption with or without a dose reduction, 50% in the REVLIMID® (lenalidomide)/dexamethasone treatment group underwent at least one additional dose interruption with or without a dose reduction compared to 21% in the placebo/dexamethasone treatment group. Most adverse events and Grade 3/4 adverse events were more frequent in patients who received the combination of REVLIMID® (lenalidomide)/dexamethasone compared to placebo/dexamethasone.

Table 6 summarizes the number and percentage of patients with Grade 1-4 adverse events reported in ≥10% of patients in either treatment group in Studies 1 and 2.

Table 6: Number of Patients with Adverse Events Reported in at Least 10% of Patients in Either Treatment Group in Studies 1 and 2 (Safety Population)

System organ class/Preferred term	Revlimid/Dex (N=346) n	(%)	Placebo/Dex (N=345) n	(%)
Subjects with at least one adverse event	346	(100.0)	344	(99.7)
Blood and Lymphatic System Disorders				
Neutropenia	96	(27.7)	16	(4.6)
Anemia NOS	84	(24.3)	60	(17.4)
Thrombocytopenia	59	(17.1)	34	(9.9)
Eye Disorders				
Vision Blurred	51	(14.7)	36	(10.4)
Gastrointestinal Disorders				
Constipation	134	(38.7)	64	(18.6)
Diarrhea NOS	101	(29.2)	85	(24.6)
Nausea	76	(22.0)	66	(19.1)
Dyspepsia	48	(13.9)	46	(13.3)
Vomiting NOS	35	(10.1)	28	(8.1)
General Disorders and Administration Site Conditions				
Fatigue	133	(38.4)	129	(37.4)
Asthenia	81	(23.4)	86	(24.9)
Pyrexia	80	(23.1)	67	(19.4)
Edema Peripheral	73	(21.1)	65	(18.8)
Infections and Infestations				
Upper Respiratory Tract Infection NOS	47	(13.6)	43	(12.5)
Pneumonia NOS	39	(11.3)	26	(7.5)
Investigations				
Weight Decreased	63	(18.2)	48	(13.9)
Metabolism and Nutrition Disorders				
Hyperglycemia NOS	52	(15.0)	49	(14.2)
Anorexia	47	(13.6)	30	(8.7)
Hypokalemia	39	(11.3)	18	(5.2)
Musculoskeletal and Connective Tissue Disorders				
Muscle Cramp	104	(30.1)	71	(20.6)
Back Pain	53	(15.3)	49	(14.2)
Muscle Weakness NOS	52	(15.0)	53	(15.4)
Arthralgia	36	(10.4)	51	(14.8)
Nervous System Disorders				
Headache	74	(21.4)	74	(21.4)
Dizziness	72	(20.8)	53	(15.4)
Tremor	68	(19.7)	24	(7.0)
Dysgeusia	46	(13.3)	32	(9.3)
Paresthesia	40	(11.6)	43	(12.5)
Psychiatric Disorders				
Insomnia	111	(32.1)	128	(37.1)
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea NOS	70	(20.2)	53	(15.4)
Cough	50	(14.5)	71	(20.6)
Skin and Subcutaneous Tissue Disorders				
Rash NOS	55	(15.9)	28	(8.1)
Vascular Disorders				
Deep Vein Thrombosis[a]	27	(7.8)	11	(3.2)
Pulmonary Embolism[a]	11	(3.2)	3	(0.9)

[a] See **WARNINGS**

Table 7 summarizes the Grade 3/4 adverse events reported in ≥2% of patients in either treatment group in Studies 1 and 2.

Table 7: Adverse Events with NCI CTC Grades 3 and 4 Reported In At Least 2% of Patients by Preferred Term and Treatment Group – (Safety Population)

	Revlimid/Dex (N=346)				Placebo/Dex (N=345)			
	Grade 3		Grade 4		Grade 3		Grade 4	
System organ class/Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Patients with at least one Grade 3 or 4 AE	225	(65.0)	25	(7.2)	186	(53.9)	31	(9.0)
Blood and Lymphatic System Disorders								
Neutropenia	60	(17.3)	13	(3.8)	8	(2.3)	2	(0.6)
Thrombocytopenia	31	(9.0)	4	(1.2)	16	(4.6)	3	(0.9)
Anemia NOS	25	(7.2)	4	(1.2)	10	(2.9)	2	(0.6)
Leukopenia NOS	12	(3.5)	0	(0.0)	1	(0.3)	0	(0.0)
Lymphopenia	8	(2.3)	0	(0.0)	4	(1.2)	0	(0.0)
Cardiac Disorders								
Atrial Fibrillation	9	(2.6)	1	(0.3)	2	(0.6)	1	(0.3)
Gastrointestinal Disorders								
Diarrhea NOS	8	(2.3)	0	(0.0)	2	(0.6)	0	(0.0)
Constipation	7	(2.0)	0	(0.0)	1	(0.3)	0	(0.0)
General Disorders and Administration Site Conditions								
Fatigue	20	(5.8)	1	(0.3)	13	(3.8)	0	(0.0)
Asthenia	14	(4.0)	0	(0.0)	16	(4.6)	0	(0.0)
Pyrexia	4	(1.2)	0	(0.0)	8	(2.3)	0	(0.0)
Infections and Infestations								
Pneumonia NOS	18	(5.2)	4	(1.2)	15	(4.3)	3	(0.9)
Metabolism and Nutrition Disorders								
Hyperglycemia NOS	22	(6.4)	4	(1.2)	19	(5.5)	7	(2.0)
Hypocalcemia	8	(2.3)	5	(1.4)	4	(1.2)	1	(0.3)
Hypokalemia	9	(2.6)	1	(0.3)	5	(1.4)	0	(0.0)
Musculoskeletal and Connective Tissue Disorders								
Muscle Weakness NOS	18	(5.2)	0	(0.0)	10	(2.9)	0	(0.0)
Nervous System Disorders								
Syncope	7	(2.0)	0	(0.0)	3	(0.9)	0	(0.0)
Neuropathy NOS	7	(2.0)	0	(0.0)	2	(0.6)	0	(0.0)
Psychiatric Disorders								
Depression	9	(2.6)	0	(0.0)	5	(1.4)	1	(0.3)
Confusional State	6	(1.7)	0	(0.0)	8	(2.3)	0	(0.0)
Respiratory, Thoracic and Mediastinal Disorders								
Dyspnea NOS	6	(1.7)	3	(0.9)	7	(2.0)	1	(0.3)
Vascular Disorders								
Deep Vein Thrombosis[a]	23	(6.6)	1	(0.3)	9	(2.6)	1	(0.3)
Pulmonary Embolism[a]	2	(0.6)	9	(2.6)	1	(0.3)	2	(0.6)

[a] See **WARNINGS**

Thrombotic Events (See WARNINGS)

In the pooled analysis, thrombotic or thromboembolic events, including deep vein thrombosis, pulmonary embolism, thrombosis, and intracranial venous sinus thrombosis, were reported more frequently in patients treated with REVLIMID® (lenalidomide)/dexamethasone combination. The number of patients experiencing a thrombotic event in the combination arm were 43/346 (12%) compared with those in the placebo/dexamethasone arm 14/345 (4%).

In these and other clinical studies of REVLIMID® (lenalidomide) in patients with multiple myeloma, the following serious adverse events (considered related to study drug treatment) not described in Table 7 were reported:

Blood and lymphatic system disorders: pancytopenia, anemia NOS aggravated

Cardiac disorders: cardiac failure congestive, atrial flutter, pulmonary edema

Endocrine disorders: adrenal insufficiency NOS, acquired hypothyroidism

Eye disorders: blindness

Gastrointestinal disorders: abdominal pain NOS, colitis pseudomembranous, gastritis NOS, gastrointestinal hemorrhage NOS, peptic ulcer hemorrhage, upper gastrointestinal hemorrhage

General disorders and administration site conditions: performance status decreased

Hepatobiliary disorders: hepatic failure, hepatitis toxic

Infections and infestations: bronchopneumonia NOS, cellulitis, *Pneumocystis carinii* pneumonia, sepsis NOS, bursitis infective NOS, cellulitis staphylococcal, *Enterobacter* bacteremia, Escherichia sepsis, gastrointestinal infection NOS, herpes zoster, herpes zoster ophthalmic, infection NOS, lung infection NOS, neutropenic sepsis, pneumonia bacterial NOS, pneumonia cytomegaloviral, pneumonia pneumococcal, pneumonia primary atypical, pneumonia staphylococcal, septic shock, streptococcal sepsis, subacute endocarditis, urinary tract infection NOS

Investigations: International normalized ratio increased, weight decreased, blood creatinine increased, body temperature increased, c-reactive protein increased, hemoglobin decreased, white blood cell count decreased

Metabolism and nutrition disorders: dehydration, diabetes mellitus NOS, diabetes with hyperosmolarity, diabetic ketoacidosis

Musculoskeletal and connective tissue disorders: myopathy steroid, back pain, myopathy

Nervous system disorders: dizziness, memory impairment, brain edema, cerebral infarction, cerebral ischemia, cerebrovascular accident, encephalitis NOS, intracranial hemorrhage NOS, intracranial venous sinus thrombosis NOS, leukoencephalopathy, somnolence, tremor

Psychiatric disorders: mental status changes, delirium, delusion NOS, insomnia, psychotic disorder NOS

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

Respiratory, thoracic and mediastinal disorders: bronchopneumopathy, hypoxia

Skin and subcutaneous tissue disorders: rash NOS, skin desquamation NOS

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

OVERDOSAGE

No cases of overdose have been reported during the clinical studies.

DOSAGE AND ADMINISTRATION

Myelodysplastic Syndromes

The recommended starting dose of REVLIMID® (lenalidomide) is 10 mg daily with water. Patients should not break, chew or open the capsules. Dosing is continued or modified based upon clinical and laboratory findings.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it would be prudent to monitor renal function.

Dose Adjustments During Treatment

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

Platelet counts

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

When Platelets	Recommended Course
Fall to <50,000/mcL	Interrupt REVLIMID® treatment
Return to ≥50,000/mcL	Resume REVLIMID® at 5 mg daily

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 and platelet transfusions	Interrupt REVLIMID® treatment
Return to ≥30,000/mcL (without hemostatic failure)	Resume REVLIMID® at 5 mg daily

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

If thrombocytopenia develops during treatment at 5 mg daily

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

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

Neutrophil counts (ANC)[+]

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

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

[+] Absolute neutrophil count

Multiple Myeloma

The recommended starting dose of REVLIMID® (lenalidomide) is 25 mg/day with water orally administered as a single 25 mg capsule on Days 1-21 of repeated 28-day cycles. Patients should not break, chew or open the capsules. The recommended dose of dexamethasone is 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. Dosing is continued or modified based upon clinical and laboratory findings.

The effect of substituting lesser strengths of REVLIMID® (lenalidomide) to achieve a 25 mg capsule dose is unknown.

Dose Adjustments During Treatment

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 lenalidomide.

Platelet counts

Thrombocytopenia

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
For each subsequent drop <30,000/mcL Return to ≥30,000/mcL	Interrupt REVLIMID® treatment Resume REVLIMID® at 5 mg less than the previous dose. Do not dose below 5 mg daily

Neutrophil counts (ANC)

Neutropenia

When Neutrophils	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
Return to ≥1,000/mcL and if other toxicity	Resume REVLIMID® at 15 mg daily
For each subsequent drop <1,000/mcL Return to ≥1,000/mcL	Interrupt REVLIMID® treatment Resume REVLIMID® at 5 mg less than the previous dose. Do not dose below 5 mg daily

Starting Dose Adjustment for Renal Impairment:

Since lenalidomide is primarily excreted unchanged by the kidney, adjustments to the starting dose of REVLIMID® (lenalidomide) are recommended to provide appropriate

drug exposure in patients with moderate or severe renal impairment and in patients on dialysis. Based on a pharmacokinetic study in patients with renal impairment due to nonmalignant conditions, lenalidomide starting dose adjustment is recommended for patients with CLcr < 60 mL/min. Non-dialysis patients with creatinine clearances less than 11 mL/min, and dialysis patients with creatinine clearances less than 7 mL/min, have not been studied. The recommendations for initial starting doses for patients with multiple myeloma (MM) and myelodysplastic syndromes (MDS) are as follows:

Starting Dose Adjustment for Renal Impairment

Category	Renal Function (Cockcroft-Gault CLcr)	Disease	
		Multiple Myeloma	Myelodysplastic Syndromes
Moderate Renal Impairment	30 ≤ CLcr < 60 mL/min	10 mg Every 24 hours	5 mg Every 24 hours
Severe Renal Impairment	CLcr < 30 ml/min (not requiring dialysis)	15 mg Every 48 hours	5 mg Every 48 hours
End Stage Renal Disease	CLcr < 30 mL/min (requiring dialysis)	5 mg Once daily. On dialysis days the dose should be administered following dialysis	5 mg 3 times a week following each dialysis

After initiation of REVLIMID® (lenalidomide) therapy, subsequent REVLIMID® (lenalidomide) dose modification should be based on individual patient treatment tolerance, as described elsewhere in this section.

Other Grade 3/4 Toxicities

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

HOW SUPPLIED

REVLIMID® (lenalidomide) 5 mg, 10 mg, 15 mg and 25 mg capsules will be supplied through the RevAssist® program. (See **INFORMATION FOR PATIENTS**)

REVLIMID® (lenalidomide) is supplied as:

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

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

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

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

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

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

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

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

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

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

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

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

Storage and Dispensing

Dispense no more than a 28-day supply.

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

Rx only.

Manufactured for Celgene Corporation

86 Morris Avenue

Summit, NJ 07901

Important Information and WARNINGS for All Patients Taking

REVLIMID® (lenalidomide)

WARNING: POTENTIAL FOR HUMAN BIRTH DEFECTS.

LENALIDOMIDE IS AN ANALOGUE OF THALIDOMIDE. THALIDOMIDE IS A KNOWN HUMAN TERATOGEN THAT CAUSES LIFE-THREATENING HUMAN BIRTH DEFECTS. IF LENALIDOMIDE IS TAKEN DURING PREGNANCY, IT MAY CAUSE BIRTH DEFECTS OR DEATH TO AN

UNBORN BABY. FEMALES SHOULD BE ADVISED TO AVOID PREGNANCY WHILE ON LENALIDOMIDE.

All Patients

- The patient understands that birth defects may occur with the use of REVLIMID® (lenalidomide).
- The patient has been warned by his/her doctor that an unborn baby may have birth defects and can even die, if a female is pregnant or becomes pregnant while taking REVLIMID® (lenalidomide).
- REVLIMID® (lenalidomide) will be prescribed ONLY for the patient and must NOT be shared with ANYONE, even someone who has similar symptoms.
- REVLIMID® (lenalidomide) must be kept out of the reach of children and should NEVER be given to females who are able to have children.
- The patient cannot donate blood while taking REVLIMID® (lenalidomide).
- The patient has read the REVLIMID® (lenalidomide) patient brochure and understands the contents, including other possible health problems from REVLIMID® (lenalidomide), "side effects."
- The patient's doctor has answered any questions the patient has asked.
- The patient must participate in a telephone survey and patient registry, while taking REVLIMID® (lenalidomide).

Female Patients of Childbearing Potential

- The patient must not take REVLIMID® (lenalidomide) if she is pregnant, breast-feeding a baby, or able to get pregnant and not using the required two methods of birth control.
- The patient confirms that she is not now pregnant, nor will she try to become pregnant during REVLIMID® (lenalidomide) therapy, during therapy interruption and for at least 4 weeks after she has completely finished taking REVLIMID® (lenalidomide).
- If the patient is able to become pregnant, she must use at least one highly effective method and one additional effective method of birth control (contraception) AT THE SAME TIME:

At least one highly effective method	AND	One additional effective method
IUD		Latex condom
Hormonal (birth control pills,		Diaphragm

injections, patch or implants) Cervical cap
Tubal ligation
Partner's vasectomy

- These birth control methods must be used for at least 4 weeks before beginning REVLIMID® (lenalidomide) therapy, during REVLIMID® (lenalidomide) therapy, during therapy interruption and for 4 weeks following discontinuation of REVLIMID® (lenalidomide) therapy.

- The patient must use these birth control methods unless she completely abstains from heterosexual sexual contact.

- If a hormonal method (birth control pills, injections, patch or implants) or IUD is not medically possible for the patient, she may use another highly effective method or two barrier methods AT THE SAME TIME.

- The patient must have a pregnancy test done by her doctor within 10-14 days and 24 hours before REVLIMID® (lenalidomide) therapy, then weekly during the first 4 weeks of REVLIMID® (lenalidomide) therapy.

- Thereafter, the patient must have a pregnancy test every 4 weeks if she has regular menstrual cycles, or every 2 weeks if her cycles are irregular while she is taking REVLIMID® (lenalidomide).

- The patient must immediately stop taking REVLIMID® (lenalidomide) and inform her doctor:

    - If she becomes pregnant while taking the drug.
    - If she misses her menstrual period, or experiences unusual menstrual bleeding.
    - If she stops using birth control.
    - If she thinks FOR ANY REASON that she may be pregnant.
    - The patient understands that if her doctor is not available, she can call 1-888-668-2528 for information on emergency contraception.

Female Patients Not of Childbearing Potential

- The patient certifies that she is not now pregnant, nor of childbearing potential as she has been postmenopausal naturally for at least 24 months (been through the change of life); or she has had a hysterectomy or bilateral oophorectomy.
- The patient or guardian certifies that a prepubertal female child is not now pregnant, nor is of childbearing potential as menstruation has not yet begun, and/or the child will not be engaging in heterosexual sexual contact for at least 4 weeks before REVLIMID® (lenalidomide) therapy, during REVLIMID®

(lenalidomide) therapy, during therapy interruption and for at least 4 weeks after stopping therapy.

Male Patients

- The patient has been told by his doctor that he must NEVER have unprotected sexual contact with a female who can become pregnant.

- Because it is not known whether REVLIMID® (lenalidomide) is present in semen, his doctor has explained that he must either completely abstain from sexual contact with females who are pregnant or able to become pregnant, or he must use a latex condom EVERY TIME he engages in any sexual contact with females who are pregnant or may become pregnant while he is taking REVLIMID® (lenalidomide) and for 4 weeks after he stops taking the drug, even if he has had a successful vasectomy.

- The patient should inform his doctor:

    - If he has had unprotected sexual contact with a female who can become pregnant.

    - If he thinks FOR ANY REASON, that his sexual partner may be pregnant.

    - The patient understands that if his doctor is not available, he can call 1-888-668-2528 for information on emergency contraception.

- The patient cannot donate semen or sperm while taking REVLIMID® (lenalidomide).

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