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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 "REVASSISTSM". UNDER THIS PROGRAM, ONLY PRESCRIBERS AND PHARMACISTS REGISTERED WITH THE PROGRAM CAN PRESCRIBE AND DISPENSE THE PRODUCT. IN ADDITION, REVLIMID MUST ONLY BE DISPENSED TO PATIENTS WHO ARE REGISTERED AND MEET ALL THE CONDITIONS OF THE REVASSISTSM PROGRAM .

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

REVASSISTSM PROGRAM DESCRIPTION

Prescribers

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

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

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

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

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

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

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

70 Any suspected fetal exposure to REVLIMID[®] (lenalidomide) should be reported to the
71 FDA *via* the MedWatch number at 1-800-FDA-1088 and also to Celgene Corporation at
72 1-888-423-5436. The patient should be referred to an obstetrician/gynecologist
73 experienced in reproductive toxicity for further evaluation and counseling.

74 **Female Patients**

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

- 78 • she understands and can reliably carry out instructions.
- 79 • she is capable of complying with the mandatory contraceptive measures, pregnancy
80 testing, patient registration, and patient survey as described in the RevAssistSM
81 program.
- 82 • she has received and understands both oral and written warnings of the potential risks
83 of taking lenalidomide during pregnancy and of exposing a fetus to the drug.
- 84 • she has received both oral and written warnings of the risk of possible contraception
85 failure and of the need to use two reliable forms of contraception simultaneously,
86 unless continuous abstinence from heterosexual sexual contact is the chosen method.
87 Sexually mature females who have not undergone a hysterectomy or who have not
88 been postmenopausal for at least 24 consecutive months (i.e., who have had menses at
89 some time in the preceding 24 consecutive months), or had a bilateral oophorectomy
90 are considered to be females of childbearing potential.
- 91 • she acknowledges, in writing, her understanding of these warnings and of the need for
92 using two reliable methods of contraception for 4 weeks prior to beginning
93 lenalidomide therapy, during lenalidomide therapy, during dose interruptions and for
94 4 weeks after discontinuation of lenalidomide therapy.
- 95 • she has had two negative pregnancy tests with a sensitivity of at least 50 mIU/mL,
96 within 10-14 days and 24 hours prior to beginning therapy.
- 97 • if the patient is between 12 and 18 years of age, her parent or legal guardian must
98 have read the educational materials and agreed to ensure compliance with the above.

99 **Male Patients**

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

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

- 108 • he has received both oral and written warnings of the risk of possible contraception
109 failure and that it is unknown whether lenalidomide is present in semen. He has been
110 instructed that he must always use a latex condom during any sexual contact with
111 females of childbearing potential, even if he has undergone a successful vasectomy.
- 112 • he acknowledges, in writing, his understanding of these warnings and of the need to
113 use a latex condom during any sexual contact with females of childbearing potential,
114 even if he has undergone a successful vasectomy. Females of childbearing potential
115 are considered to be sexually mature females who have not undergone a
116 hysterectomy, have not had a bilateral oophorectomy or who have not been
117 postmenopausal for at least 24 consecutive months (i.e., who have had menses at any
118 time in the preceding 24 consecutive months).
- 119 • if the patient is between 12 and 18 years of age, his parent or legal guardian must
120 have read the educational material and agreed to ensure compliance with the above.

121 **HEMATOLOGIC TOXICITY (NEUTROPENIA AND THROMBOCYTOPENIA)**

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

131 **DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM**

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

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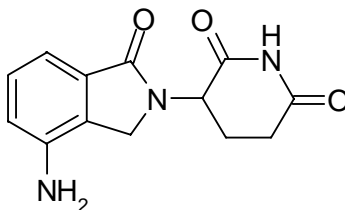
144 You can get the information about REVLIMID[®] and the RevAssistSM program on
145 the internet at www.REVLIMID.com or by calling the manufacturer's toll free
146 number 1-888-423-5436.

147 DESCRIPTION

148 REVLIMID[®] (lenalidomide), a thalidomide analogue, is an immunomodulatory agent
149 with anti-angiogenic and anti-neoplastic properties. The chemical name is 3-(4-amino-1-
150 oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical
151 structure:

152

Chemical Structure of Lenalidomide



153

154 3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

155 The empirical formula for lenalidomide is C₁₃H₁₃N₃O₃, and the gram molecular weight is
156 259.3.

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

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

170 CLINICAL PHARMACOLOGY

171 Mechanism of Action:

172 The mechanism of action of lenalidomide remains to be fully characterized.
173 Lenalidomide possesses anti-neoplastic, immunomodulatory and antiangiogenic
174 properties. Lenalidomide inhibited the secretion of pro-inflammatory cytokines and
175 increased the secretion of anti-inflammatory cytokines from peripheral blood
176 mononuclear cells. Lenalidomide inhibited cell proliferation with varying effectiveness
177 (IC50s) in some but not all cell lines. Of cell lines tested, lenalidomide was effective in

178 inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion
179 of one chromosome 5) but was much less effective in inhibiting growth of KG-1 cells
180 (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell
181 lines without chromosome 5 deletions. Lenalidomide inhibited the growth of multiple
182 myeloma cells from patients, as well as MM.1S cells (a human multiple myeloma cell
183 line), by inducing cell cycle arrest and apoptosis.

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

186 **Pharmacokinetics and Drug Metabolism:**

187 **Absorption:**

188 Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration
189 with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose.
190 Co-administration with food does not alter the extent of absorption (AUC) but does
191 reduce the maximal plasma concentration (C_{max}) by 36%. The pharmacokinetic
192 disposition of lenalidomide is linear. C_{max} and AUC increase proportionately with
193 increases in dose. Multiple dosing at the recommended dose-regimen does not result in
194 drug accumulation.

195 Pharmacokinetic sampling in myelodysplastic syndromes (MDS) patients was not
196 performed. In multiple myeloma patients maximum plasma concentrations occurred
197 between 0.5 and 4.0 hours post-dose both on Days 1 and 28. AUC and C_{max} values
198 increase proportionally with dose following single and multiple doses. Exposure (AUC)
199 in multiple myeloma patients is 57% higher than in healthy male volunteers.

200 **Pharmacokinetic Parameters:**

201 **Distribution:**

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

203 **Metabolism and Excretion:**

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

208 **Special Populations:**

209 *Patients with Renal Insufficiency:* The pharmacokinetics of lenalidomide in MDS patients
210 with renal dysfunction has not been determined. In multiple myeloma patients, those with
211 mild renal impairment had an AUC 56% greater than those with normal renal function.
212 (See **PRECAUTIONS: Renal Impairment**).

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

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

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

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

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

220 **CLINICAL STUDIES**

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

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

229 This major study enrolled 148 patients who had RBC transfusion dependent anemia.
230 RBC-transfusion dependence was defined as having received ≥ 2 units of RBCs within 8
231 weeks prior to study treatment. The study enrolled patients with absolute neutrophil
232 counts (ANC) ≥ 500 cells/mm³, platelet counts $\geq 50,000$ /mm³, serum creatinine ≤ 2.5
233 mg/dL, serum SGOT/AST or SGPT/ALT ≤ 3.0 x upper limit of normal (ULN), and
234 serum direct bilirubin ≤ 2.0 mg/dL. Granulocyte colony-stimulating factor was permitted
235 for patients who developed neutropenia or fever in association with neutropenia. Baseline
236 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 \geq 2.5); Combined score = (Marrow blast score + Karyotype score + Cytopenia score)

[b] French-American-British (FAB) classification of MDS.

237 The frequency of RBC-transfusion independence was modified from the International
238 Working Group (IWG) response criteria for MDS. RBC transfusion independence was
239 defined as the absence of any RBC transfusion during any consecutive “rolling” 56 days
240 (8 weeks) during the treatment period.

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

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

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

249 The dose of REVLIMID[®] (lenalidomide) was reduced or interrupted at least once due to
250 an adverse event in 118 (79.7%) of the 148 patients; the median time to the first dose
251 reduction or interruption was 21 days (mean, 35.1 days; range, 2-253 days), and the
252 median duration of the first dose interruption was 22 days (mean, 28.5 days; range, 2-265
253 days). A second dose reduction or interruption due to adverse events was required in 50
254 (33.8%) of the 148 patients. The median interval between the first and second dose
255 reduction or interruption was 51 days (mean, 59.7 days; range, 15-205 days) and the
256 median duration of the second dose interruption was 21 days (mean, 26 days; range, 2-
257 148 days).

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

260 **Multiple Myeloma**

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

266 In both studies, patients in the REVLIMID[®] (lenalidomide)/dexamethasone group took
267 25 mg of REVLIMID[®] (lenalidomide) orally once daily on Days 1 to 21 and a matching
268 placebo capsule once daily on Days 22 to 28 of each 28-day cycle. Patients in the
269 placebo/dexamethasone group took 1 placebo capsule on Days 1 to 28 of each 28-day

270 cycle. Patients in both treatment groups took 40 mg of dexamethasone orally once daily
271 on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy.
272 The dose of dexamethasone was reduced to 40 mg orally once daily on Days 1 to 4 of
273 each 28-day cycle after the first 4 cycles of therapy. In both studies, treatment was to
274 continue until disease progression.

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

278 Table 2 summarizes the baseline patient and disease characteristics in the two studies. In
279 both studies, baseline demographic and disease-related characteristics were comparable
280 between the REVLIMID[®] (lenalidomide)/dexamethasone and placebo/dexamethasone
281 groups.

282 **Table 2 Baseline Demographic and Disease-related Characteristics - 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	64	62	63	64
Min, Max	36, 86	37, 85	33, 84	40, 82
Sex				
Male	102 (60%)	101 (59%)	104 (59%)	103 (59%)
Female	68 (40%)	70 (41%)	72 (41%)	72 (41%)
Race/Ethnicity				
White	134 (79%)	143 (84%)	172 (98%)	175 (100%)
Other	36 (21%)	28 (16%)	4 (2%)	0 (0%)
ECOG Performance Status 0-1	151 (89%)	163 (95%)	150 (85%)	144 (82%)
Disease Characteristics				
Baseline Multiple Myeloma Stage (Durie-Salmon)				
I	2%	2%	6%	5%
II	31%	31%	28%	33%
III	67%	67%	65%	63%
Baseline Creatinine (mg/dL)				
Median	1.0	1.0	0.9	0.9
Min, Max	0.4, 2.6	0.5, 2.4	0.3, 2.3	0.5, 2.3
B2-microglobulin (mg/L)				
Median	3.7	3.3	3.4	3.3
Min, Max	1.1, 45	1.3, 15.2	1.0, 14.4	1.3, 25.3
Number of Prior Therapies				
No. of Prior Antimyeloma Therapies				
1	38%	37%	32%	33%
≥ 2	62%	63%	68%	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%

283

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

287
288 Preplanned interim analyses of both studies showed that the combination of REVLIMID[®]
289 (lenalidomide)/dexamethasone was significantly superior to dexamethasone alone for
290 TTP. The studies were unblinded to allow patients in the placebo/dexamethasone group
291 to receive treatment with the REVLIMID[®] (lenalidomide)/dexamethasone combination.

292
293 Table 3 summarizes TTP and response rates based on the best response assessments for
294 Studies 1 and 2.

295
296 **Table 3: Summary of Efficacy Analysis — Studies 1 and 2**

	<u>Study 1</u>		<u>Study 2</u>	
	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 ²]	19.9 [16, 22]	NE ²	20 [19.9, 21.6]
Hazard Ratio ³ [95% CI]	0.356 [0.257,0.494]		0.392 [0.274,0.562]	
Log-rank Test p-Value ¹	<0.0001		<0.0001	
Response				
Complete Response (CR) n (%)	14 (8)	1 (1)	14 (8)	1 (1)
Partial Responses (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]	

297
298 ¹ The p-value is based on a one-tailed unstratified log rank test.

299 ² NE, Not Estimable due to short follow-up.

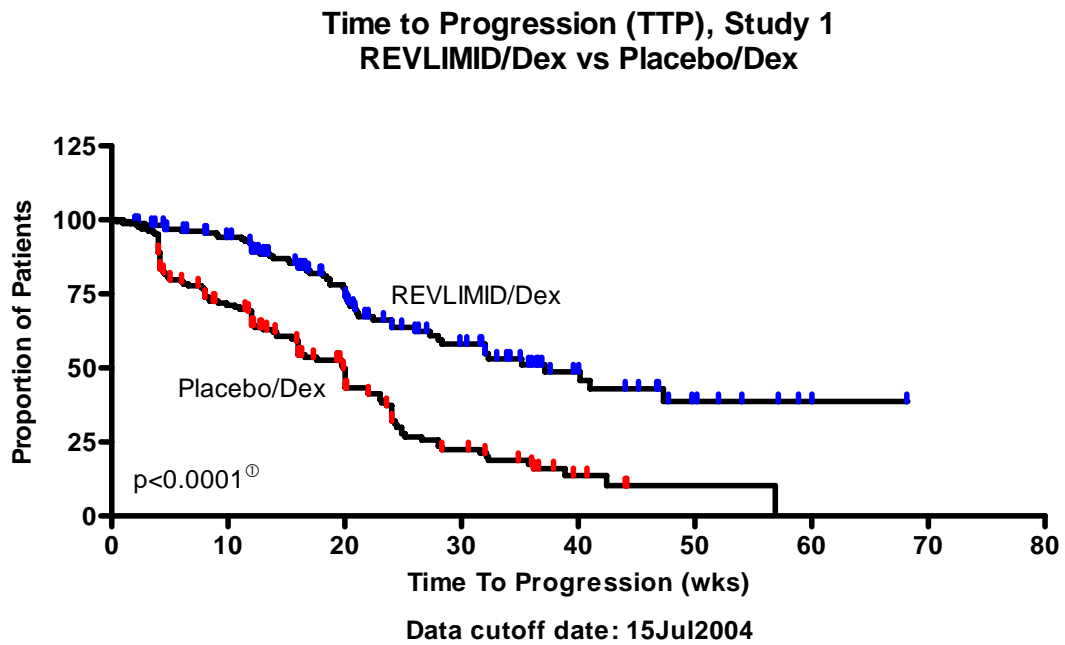
300 ³ Hazard Ratio of Revlimid/Dexamethasone to Placebo/Dexamethasone

301
302 Figures 1 and 2 depict the Kaplan-Meier estimates of TTP in Studies 1 and 2,
303 respectively.

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

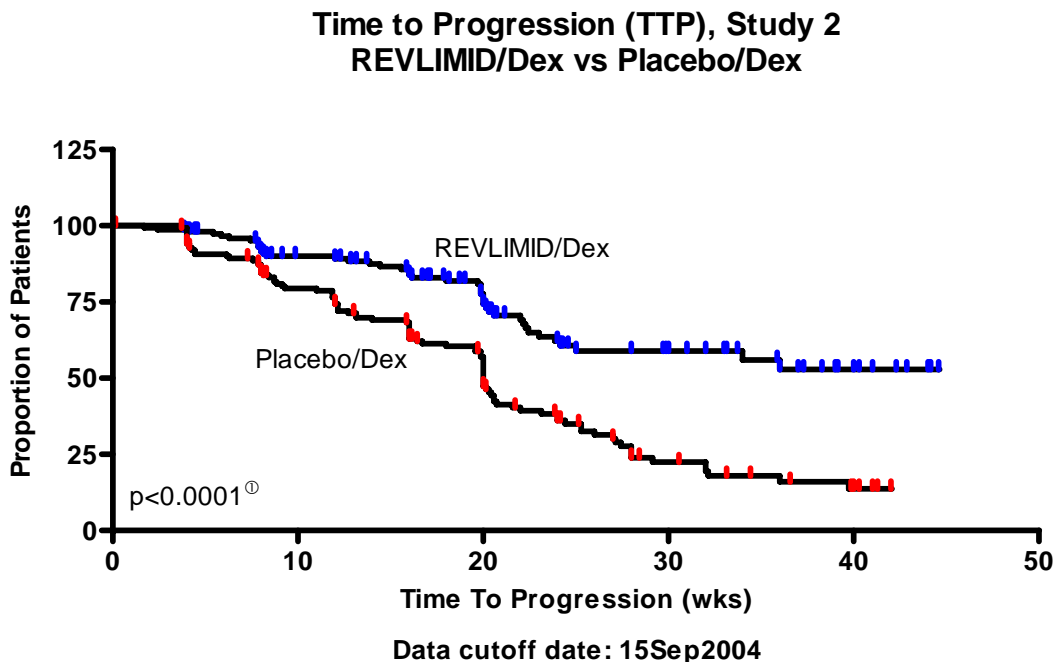


[Ⓛ] p-value from log-rank test

309
310
311
312

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

313 Figure 2: Kaplan-Meier Estimate of Time to Progression — Study 2
314



^① p-value from log-rank test

315
316 The median duration of Study 2 follow-up was 22.3 weeks.

317 INDICATIONS AND USAGE:

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

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

324 CONTRAINDICATIONS:

325 **Pregnancy Category X: (See ‘BOXED WARNING’)**

326 Due to its structural similarities to thalidomide, a known human teratogen, lenalidomide
327 is contraindicated in pregnant women and women capable of becoming pregnant. (See
328 **BOXED WARNINGS**.) When there is no alternative, females of childbearing potential
329 may be treated with lenalidomide provided adequate precautions are taken to avoid
330 pregnancy. Females must commit either to abstain continuously from heterosexual
331 sexual intercourse or to use two methods of reliable birth control, including at least one
332 highly effective method (e.g., IUD, hormonal contraception, tubal ligation, or partner’s

333 vasectomy) and one additional effective method (e.g., latex condom, diaphragm, or
334 cervical cap), beginning 4 weeks prior to initiating treatment with REVLIMID[®]
335 (lenalidomide), during therapy with REVLIMID[®] (lenalidomide), during therapy delay,
336 and continuing for 4 weeks following discontinuation of REVLIMID[®] (lenalidomide)
337 therapy. If hormonal or IUD contraception is medically contraindicated, two other
338 effective or highly effective methods may be used.

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

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

352 **WARNINGS:**

353 **Pregnancy Category X: (See ‘BOXED WARNING’ and CONTRAINDICATIONS)**

354 REVLIMID[®] (lenalidomide) is an analogue of thalidomide. Thalidomide is a known
355 human teratogen that causes life-threatening human birth defects. REVLIMID[®]
356 (lenalidomide) may cause fetal harm when administered to a pregnant female. Females of
357 childbearing potential should be advised to avoid pregnancy while on REVLIMID[®]
358 (lenalidomide). Two effective contraceptive methods should be used during therapy,
359 during therapy interruptions and for at least 4 weeks after completing therapy.

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

361 Because of this potential toxicity and to avoid fetal exposure to REVLIMID[®]
362 (lenalidomide), REVLIMID[®] (lenalidomide) is only available under a special restricted
363 distribution program. This program is called "RevAssistSM".

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

366 An embryo-fetal development study in rats revealed no teratogenic effects at the highest
367 dose of 500 mg/kg (approximately 600 times the human dose of 10 mg based on body
368 surface area). At 100, 300 or 500 mg/kg/day there was minimal maternal toxicity that
369 included slight, transient, reduction in mean body weight gain and food intake. However

370 this animal model may not adequately address the full spectrum of the potential embryo-
371 fetal developmental effects of lenalidomide.

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

377 Reproductive effects of lenalidomide have not been thoroughly assessed. The structural
378 similarity of lenalidomide to thalidomide, a known human teratogen, suggests a potential
379 risk to the developing fetus.

380 **HEMATOLOGIC TOXICITY (NEUTROPENIA AND THROMBOCYTOPENIA):**

381 **This drug is associated with significant neutropenia and thrombocytopenia.**

382 **Eighty percent of patients with del 5q MDS had to have a dose delay or reduction**
383 **during the major study for the indication. Thirty-four percent of patients had to**
384 **have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in**
385 **80% of patients enrolled in the study. In the 48% of patients who developed Grade**
386 **3 or 4 neutropenia, the median time to onset was 42 days (range, 14 – 411 days), and**
387 **the median time to documented recovery was 17 days (range, 2 – 170 days). In the**
388 **54% of patients who developed Grade 3 or 4 thrombocytopenia, the median time to**
389 **onset was 28 days (range, 8 - 290 days), and the median time to documented**
390 **recovery was 22 days (range, 5 – 224 days). Patients on therapy for del 5q**
391 **myelodysplastic syndromes should have their complete blood counts monitored**
392 **weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients**
393 **may require dose interruption and/or reduction. Patients may require use of blood**
394 **product support and/or growth factors. See DOSAGE AND ADMINISTRATION.**

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

402 **DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM:**

403 **This drug has demonstrated a significantly increased risk of DVT and PE in**
404 **patients with multiple myeloma who were treated with REVLIMID[®] (lenalidomide)**
405 **combination therapy. Patients and physicians are advised to be observant for the**
406 **signs and symptoms of thromboembolism. Patients should be instructed to seek**
407 **medical care if they develop symptoms such as shortness of breath, chest pain, or**
408 **arm or leg swelling. It is not known whether prophylactic anticoagulation or**

409 **antiplatelet therapy prescribed in conjunction with REVLIMID[®] (lenalidomide)**
410 **may lessen the potential for venous thromboembolic events. The decision to take**
411 **prophylactic measures should be done carefully after an assessment of an individual**
412 **patient's underlying risk factors. See ADVERSE REACTIONS Table 7.**

413

414 **PRECAUTIONS:**

415 **General:**

416 No formal studies have been conducted in patients with renal impairment. This drug is
417 known to be excreted by the kidney, and the risk of adverse reactions to this drug may be
418 greater in patients with impaired renal function.

419 **Information for Patients:**

420 Patients should be counseled on lenalidomide's potential risk of teratogenicity due to its
421 structural similarity to thalidomide. Patients may only acquire a prescription for
422 REVLIMID[®] (lenalidomide) therapy through a controlled distribution program
423 (RevAssistSM) through contracted pharmacies. Female patients of childbearing potential
424 will be educated and counseled on the requirements of the RevAssistSM program and the
425 precautions to be taken to preclude fetal exposure to REVLIMID[®] (lenalidomide).
426 Patients should become familiar with the REVLIMID[®] RevAssistSM educational
427 materials, Patient Medication Guide, and direct any questions to their physician or
428 pharmacist prior to starting REVLIMID[®] (lenalidomide) therapy.

429 **Laboratory tests:**

430 The MDS clinical study enrolled patients with absolute neutrophil counts (ANC) ≥ 500
431 cells/mm³, platelet counts $\geq 50,000/\text{mm}^3$, serum creatinine ≤ 2.5 mg/dL, serum
432 SGOT/AST or SGPT/ALT ≤ 3.0 x upper limit of normal (ULN), and serum direct
433 bilirubin ≤ 2.0 mg/dL. A complete blood cell count (CBC), including white blood cell
434 count with differential, platelet count, hemoglobin, and hematocrit should be performed
435 weekly for the first 8 weeks of REVLIMID[®] (lenalidomide) treatment and monthly
436 thereafter to monitor for cytopenias.

437 The multiple myeloma studies 1 and 2 enrolled patients with absolute neutrophil counts
438 (ANC) ≥ 1000 cells/mm³, platelet counts $\geq 75,000/\text{mm}^3$, serum creatinine ≤ 2.5 mg/dL,
439 serum SGOT/AST or SGPT/ALT ≤ 3.0 x upper limit of normal (ULN), and serum direct
440 bilirubin ≤ 2.0 mg/dL. A CBC should be performed every two weeks for the first three
441 months and at least monthly thereafter to monitor for cytopenias.

442 **Drug Interactions:**

443 Results from human in vitro metabolism studies and nonclinical studies show that
444 REVLIMID[®] (lenalidomide) is neither metabolized by nor inhibits or induces the

445 cytochrome P450 pathway suggesting that lenalidomide is not likely to cause or be
446 subject to P450-based metabolic drug interactions in man.

447 Co-administration of multiple doses of 10 mg of lenalidomide had no effect on the single
448 dose pharmacokinetics of R- and S- **warfarin**. Co-administration of single 25-mg dose
449 **warfarin** had no effect on the pharmacokinetics of total lenalidomide. Expected changes
450 in laboratory assessments of PT and INR were observed after **warfarin** administration,
451 but these changes were not affected by concomitant lenalidomide administration.

452 When **digoxin** was co-administered with lenalidomide the **digoxin** AUC was not
453 significantly different, however, the **digoxin** C_{max} was increased by 14%. Periodic
454 monitoring of **digoxin** plasma levels, in accordance with clinical judgment and based on
455 standard clinical practice in patients receiving this medication, is recommended during
456 administration of lenalidomide.

457 **Carcinogenesis, mutagenesis, impairment of fertility:**

458 Carcinogenicity: Carcinogenicity studies with lenalidomide have not been conducted.

459 Mutagenesis: Lenalidomide did not induce mutation in the Ames test, chromosome
460 aberrations in cultured human peripheral blood lymphocytes, or mutation at the
461 thymidine kinase (tk) locus of mouse lymphoma L5178Y cells. Lenalidomide did not
462 increase morphological transformation in Syrian Hamster Embryo assay or induce
463 micronuclei in the polychromatic erythrocytes of the bone marrow of male rats.

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

468 **Pregnancy:**

469 **Pregnancy Category X: (See ‘BOXED WARNINGS’ and CONTRAINDICATIONS)**

470 Because of the structural similarity to thalidomide, a known human teratogen, and the
471 lack of sufficient information regarding lenalidomide’s teratogenic potential,
472 REVLIMID[®] (lenalidomide) is contraindicated in females who are or may become
473 pregnant and who are not using the two required types of birth control or who are not
474 continually abstaining from reproductive heterosexual sexual intercourse. REVLIMID[®]
475 (lenalidomide) should not be used by females who are pregnant or who could become
476 pregnant while taking the drug. If pregnancy does occur during treatment, the drug
477 should be immediately discontinued. Under these conditions, the patient should be
478 referred to an obstetrician / gynecologist experienced in reproductive toxicity for further
479 evaluation and counseling. Any suspected fetal exposure to REVLIMID[®] (lenalidomide)
480 should be reported to the FDA via the MedWatch program at 1-800-FDA-1088 and also
481 to Celgene Corporation at 1-888-423-5436.

482 **Use in Nursing Mothers:**

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

487 **Pediatric Use:**

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

490 **Geriatric Use:**

491 REVLIMID[®] (lenalidomide) has been used in del 5q MDS clinical trials in patients up to
492 95 years of age.

493 Of the 148 patients with del 5q MDS enrolled in the major study, 38% were age 65 and
494 over, while 33% were age 75 and over. Although the overall frequency of adverse events
495 (100%) was the same in patients over 65 years of age as in younger patients, the
496 frequency of serious adverse events was higher in patients over 65 years of age than in
497 younger patients (54% vs. 33%). A greater proportion of patients over 65 years of age
498 discontinued from the clinical studies because of adverse events than the proportion of
499 younger patients (27% vs. 16%). No differences in efficacy were observed between
500 patients over 65 years of age and younger patients.

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

503

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

513

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

518 **Renal Impairment:**

519 This drug is known to be substantially excreted by the kidney, and the risk of toxic
520 reactions to this drug is expected to be greater in patients with impaired renal function.
521 Patients with renal insufficiency were excluded from the clinical trials, and those who
522 developed renal insufficiency during the clinical trials had the drug held. Care should be
523 taken in dose selection, and it would be prudent to monitor renal function.

524 **ADVERSE REACTIONS:**

525 **Myelodysplastic Syndromes**

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

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

Table 4 Summary of adverse events reported in $\geq 5\%$ 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)
DYSPNOEA 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)
HYPOASTHESIA	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	
HYPOKALAEMIA	16 (10.8)
ANOREXIA	15 (10.1)
HYPOMAGNEAEMIA	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.

541

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 GR 3 / 4 AE	131 (88.5)
NEUTROPENIA	79 (53.4)
THROMBOCYTOPENIA	74 (50.0)
PNEUMONIA NOS	11 (7.4)
RASH NOS	10 (6.8)
ANAEMIA 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 $\geq 1\%$ 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.	

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

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

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

553 **Ear and labyrinth disorders:** vertigo

554 **Endocrine disorders:** Basedow's disease

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

- 561 **General disorders and administration site conditions:** disease progression NOS, fall,
562 gait abnormal, intermittent pyrexia, nodule, rigors, sudden death
- 563 **Hepatobiliary disorders:** hyperbilirubinemia, cholecystitis acute NOS, cholecystitis
564 NOS, hepatic failure
- 565 **Immune system disorders:** hypersensitivity NOS
- 566 **Infections and infestations:** infection NOS, bacteremia, central line infection, clostridial
567 infection NOS, ear infection NOS, *Enterobacter* sepsis, fungal infection NOS, herpes
568 viral infection NOS, influenza, kidney infection NOS, *Klebsiella* sepsis, lobar pneumonia
569 NOS, localized infection, oral infection, *Pseudomonas* infection NOS, septic shock,
570 sinusitis acute NOS, sinusitis NOS, *Staphylococcal* infection, urosepsis
- 571 **Injury, poisoning and procedural complications:** femur fracture, transfusion reaction,
572 cervical vertebral fracture, femoral neck fracture, fractured pelvis NOS, hip fracture,
573 overdose NOS, post procedural hemorrhage, rib fracture, road traffic accident, spinal
574 compression fracture
- 575 **Investigations:** blood creatinine increased, culture NOS negative, hemoglobin decreased,
576 liver function tests NOS abnormal, troponin I increased
- 577 **Metabolism and nutrition disorders:** dehydration, gout, hypernatremia, hypoglycemia
578 NOS
- 579 **Musculoskeletal and connective tissue disorders:** arthritis NOS, arthritis NOS
580 aggravated, gouty arthritis, neck pain, chondrocalcinosis pyrophosphate
- 581 **Neoplasms benign, malignant and unspecified:** acute leukemia NOS, acute myeloid
582 leukemia NOS, bronchoalveolar carcinoma, lung cancer metastatic, lymphoma NOS,
583 prostate cancer metastatic
- 584 **Nervous system disorders:** cerebrovascular accident, aphasia, cerebellar infarction,
585 cerebral infarction, depressed level of consciousness, dysarthria, migraine NOS, spinal
586 cord compression NOS, subarachnoid hemorrhage NOS, transient ischemic attack
- 587 **Psychiatric disorders:** confusional state
- 588 **Renal and urinary disorders:** renal failure NOS, hematuria, renal failure acute,
589 azotemia, calculus ureteric, renal mass NOS
- 590 **Reproductive system and breast disorders:** pelvic pain NOS
- 591 **Respiratory, thoracic and mediastinal disorders:** bronchitis NOS, chronic obstructive
592 airways disease exacerbated, respiratory failure, dyspnea exacerbated, interstitial lung
593 disease, lung infiltration NOS, wheezing
- 594 **Skin and subcutaneous tissue disorders:** acute febrile neutrophilic dermatosis

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

597 **Multiple Myeloma**

598

599 Data were evaluated from 691 patients in two studies who received at least one dose of
600 REVLIMID[®] (lenalidomide)/dexamethasone (346 patients) or placebo/dexamethasone
601 (345 patients). In the REVLIMID[®] (lenalidomide) /dexamethasone treatment group, 151
602 patients (45%) underwent at least one dose interruption with or without a dose reduction
603 of REVLIMID[®] (lenalidomide) compared to 21% in the placebo/dexamethasone
604 treatment group. Of these patients who had one dose interruption with or without a dose
605 reduction, 50% in the REVLIMID[®] (lenalidomide) /dexamethasone treatment group
606 underwent at least one additional dose interruption with or without a dose reduction
607 compared to 21% in the placebo/dexamethasone treatment group. Most adverse events
608 and Grade 3/4 adverse events were more frequent in patients who received the
609 combination of REVLIMID[®] (lenalidomide)/dexamethasone compared to
610 placebo/dexamethasone.

611

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

614

615

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		Placebo/Dex (N=345)	
	n	(%)	n	(%)
Subjects with at least one adverse event				
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
NEUTROPENIA	96	(27.7)	16	(4.6)
ANAEMIA 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)
DIARRHOEA 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)
OEDEMA 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				
HYPERGLYCAEMIA NOS	52	(15.0)	49	(14.2)
ANOREXIA	47	(13.6)	30	(8.7)
HYPOKALAEMIA	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)
PARAESTHESIA	40	(11.6)	43	(12.5)
PSYCHIATRIC DISORDERS				
INSOMNIA	111	(32.1)	128	(37.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
DYSPNOEA 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)

616

^a See WARNINGS

617

618 Table 7 summarizes the Grade 3/4 adverse events reported in $\geq 2\%$ of patients in either
619 treatment group in Studies 1 and 2.

System organ class/ Preferred term	Revlimid/Dex (N=346)		Placebo/Dex (N=345)	
	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 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)
ANAEMIA 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				
DIARRHOEA 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				
HYPERGLYCAEMIA NOS	22 (6.4)	4 (1.2)	19 (5.5)	7 (2.0)
HYPOCALCAEMIA	8 (2.3)	5 (1.4)	4 (1.2)	1 (0.3)
HYPOKALAEMIA	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				
DYSPNOEA 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)

620 ^a See WARNINGS

621

622 **Thrombotic Events (See WARNINGS)**

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

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

632 **Blood and lymphatic system disorders:** pancytopenia, anemia NOS aggravated

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

634 **Endocrine disorders:** adrenal insufficiency NOS, acquired hypothyroidism

635 **Eye disorders:** blindness

636 **Gastrointestinal disorders:** abdominal pain NOS, colitis pseudomembranous, gastritis
637 NOS, gastrointestinal hemorrhage NOS, peptic ulcer hemorrhage, upper gastrointestinal
638 hemorrhage

639 **General disorders and administration site conditions:** performance status decreased

640 **Hepatobiliary disorders:** hepatic failure, hepatitis toxic

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

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

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

653 **Musculoskeletal and connective tissue disorders:** myopathy steroid, back pain,
654 myopathy

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

- 659 **Psychiatric disorders:** mental status changes, delirium, delusion NOS, insomnia,
660 psychotic disorder NOS
- 661 **Renal and urinary disorders:** Fanconi syndrome acquired, hematuria, renal failure
662 acute, renal failure NOS, renal tubular necrosis, urinary retention
- 663 **Respiratory, thoracic and mediastinal disorders:** bronchopneumopathy, hypoxia
- 664 **Skin and subcutaneous tissue disorders:** rash NOS, skin desquamation NOS
- 665 **Vascular system disorders:** phlebitis NOS, venous thrombosis NOS limb, circulatory
666 collapse, hypertension NOS, hypotension NOS, orthostatic hypotension, peripheral
667 ischemia

668 **OVERDOSAGE**

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

670 **DOSAGE AND ADMINISTRATION**

671 **Myelodysplastic Syndromes**

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

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

679 **Dose Adjustments During Treatment:**

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

682 **Platelet counts**

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

If baseline $\geq 100,000/\text{mcL}$

When Platelets	Recommended Course
Fall to $< 50,000/\text{mcL}$	Interrupt REVLIMID [®] treatment
Return to $\geq 50,000/\text{mcL}$	Resume REVLIMID [®] at 5 mg daily

If baseline $< 100,000/\text{mcL}$

When Platelets	Recommended Course
Fall to 50% of the baseline value	Interrupt REVLIMID [®] treatment
If baseline $\geq 60,000/\text{mcL}$ and returns to $\geq 50,000/\text{mcL}$	Resume REVLIMID [®] at 5 mg daily

	If baseline <60,000/mcL and returns to $\geq 30,000$ /mcL	Resume REVLIMID [®] at 5 mg daily
684		
685	<u>If thrombocytopenia develops AFTER 4 weeks of starting treatment at 10 mg daily</u>	
	When Platelets	Recommended Course
	$<30,000$ /mcL or $<50,000$ /mcL and platelet transfusions	Interrupt REVLIMID [®] treatment
	Return to $\geq 30,000$ /mcL (without hemostatic failure)	Resume REVLIMID [®] at 5 mg daily
686	Patients who experience thrombocytopenia at 5 mg daily should have their dosage	
687	adjusted as follows:	
688	<u>If thrombocytopenia develops during treatment at 5 mg daily</u>	
	When Platelets	Recommended Course
	$<30,000$ /mcL or $<50,000$ /mcL and platelet transfusions	Interrupt REVLIMID [®] treatment
	Return to $\geq 30,000$ /mcL (without hemostatic failure)	Resume REVLIMID [®] at 5 mg every other day
689	Patients who are dosed initially at 10 mg and experience neutropenia should have their	
690	dosage adjusted as follows:	
691	Neutrophil counts (ANC)⁺	
692	<u>If neutropenia develops WITHIN 4 weeks of starting treatment at 10 mg daily</u>	
	<u>If baseline ANC $\geq 1,000$/mcL</u>	
	When Neutrophils	Recommended Course
	Fall to <750 /mcL	Interrupt REVLIMID [®] treatment
	Return to $\geq 1,000$ /mcL	Resume REVLIMID [®] at 5 mg daily
	<u>If baseline ANC $<1,000$/mcL</u>	
	When Neutrophils	Recommended Course
	Fall to <500 /mcL	Interrupt REVLIMID [®] treatment
	Return to ≥ 500 /mcL	Resume REVLIMID [®] at 5 mg daily
693		
694	<u>If neutropenia develops AFTER 4 weeks of starting treatment at 10 mg daily</u>	
	When Neutrophils	Recommended Course
	<500 /mcL for ≥ 7 days or <500 /mcL associated with fever ($\geq 38.5^{\circ}\text{C}$)	Interrupt REVLIMID [®] treatment
	Return to ≥ 500 /mcL	Resume REVLIMID [®] at 5 mg daily
695	Patients who experience neutropenia at 5 mg daily should have their dosage adjusted as	
696	follows:	

697 **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

698 + Absolute neutrophil count

699

700 **Multiple Myeloma**

701 The recommended starting dose of REVLIMID[®] (lenalidomide) is 25 mg/day with water
702 orally administered as a single 25 mg capsule on Days 1-21 of repeated 28-day cycles.
703 Patients should not break, chew or open the capsules. The recommended dose of
704 dexamethasone is 40 mg/day on Days 1-4, 9-12, and 17-20 of each 28-day cycle for the
705 first 4 cycles of therapy and then 40 mg/day orally on Days 1-4 every 28 days. Dosing is
706 continued or modified based upon clinical and laboratory findings.

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

709 **Dose Adjustments During Treatment:**

710 Dose modification guidelines, as summarized below are recommended to manage Grade
711 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicity judged to be
712 related to lenalidomide.

713 **Platelet counts**

714 **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	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

715 **Neutrophil counts (ANC)**

716 **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 \geq 1,000/mcL	Interrupt REVLIMID [®] treatment Resume REVLIMID [®] at 5 mg less than the previous dose. Do not dose below 5 mg daily
717	
718	Other Grade 3/4 Toxicities
719	For other Grade 3/4 toxicities judged to be related to lenalidomide, hold treatment and
720	restart at next lower dose level when toxicity has resolved to \leq Grade 2.
721	HOW SUPPLIED
722	REVLIMID [®] (lenalidomide) 5 mg, 10 mg, 15 mg and 25 mg capsules will be supplied
723	through the RevAssist SM program. (See INFORMATION FOR PATIENTS)
724	REVLIMID [®] (lenalidomide) is supplied as:
725	White opaque capsules imprinted “REV” on one half and “5 mg” on the other half in
726	black ink:
727	5 mg bottles of 30 (NDC 59572-405-30)
728	5 mg bottles of 100 (NDC 59572-405-00)
729	Blue/green and pale yellow opaque capsules imprinted “REV” on one half and “10 mg”
730	on the other half in black ink:
731	10 mg bottles of 30 (NDC 59572-410-30)
732	10 mg bottles of 100 (NDC 59572-410-00)
733	Powder blue and white opaque capsules imprinted “REV” on one half and “15 mg” on
734	the other half in black ink:
735	15 mg bottles of 21 (NDC 59572-415-21)
736	15 mg bottles of 100 (NDC 59572-415-00)
737	White opaque capsules imprinted “REV” on one half and “25 mg” on the other half in
738	black ink:
739	25 mg bottles of 25 (NDC 59572-425-25)
740	25 mg bottles of 100 (NDC 59572-425-00)
741	Storage and Dispensing
742	Dispense no more than a 28-day supply.

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

745 Rx only.

746 Manufactured for Celgene Corporation

747 86 Morris Avenue

748 Summit, NJ 07901

749 **Important Information and Warnings for All Patients Taking REVLIMID[®]**
750 **(lenalidomide)**

751 **WARNING: POTENTIAL FOR HUMAN BIRTH DEFECTS.**

752 **LENALIDOMIDE IS AN ANALOGUE OF THALIDOMIDE. THALIDOMIDE IS**
753 **A KNOWN HUMAN TERATOGEN THAT CAUSES LIFE-THREATENING**
754 **HUMAN DEFECTS. IF LENALIDOMIDE IS TAKEN DURING PREGNANCY,**
755 **IT MAY CAUSE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY.**
756 **FEMALES SHOULD BE ADVISED TO AVOID PREGNANCY WHILE ON**
757 **LENALIDOMIDE.**

758 **All Patients**

- 759 • The patient understands that birth defects may occur with the use of REVLIMID[®]
760 (lenalidomide).
- 761 • The patient has been warned by his/her doctor that an unborn baby may have birth
762 defects and can even die, if a female is pregnant or becomes pregnant while taking
763 REVLIMID[®] (lenalidomide).
- 764 • REVLIMID[®] (lenalidomide) will be prescribed ONLY for the patient and must NOT
765 be shared with ANYONE, even someone who has similar symptoms.
- 766 • REVLIMID[®] (lenalidomide) must be kept out of the reach of children and should
767 NEVER be given to females who are able to have children.
- 768 • The patient cannot donate blood while taking REVLIMID[®] (lenalidomide).
- 769 • The patient has read the REVLIMID[®] (lenalidomide) patient brochure and
770 understands the contents, including other possible health problems from REVLIMID[®]
771 (lenalidomide), “side effects.”
- 772 • The patient’s doctor has answered any questions the patient has asked.
- 773 • The patient must participate in a telephone survey and patient registry, while taking
774 REVLIMID[®] (lenalidomide).

775 **Female Patients of Childbearing Potential**

- 776 • The patient must not take REVLIMID[®] (lenalidomide) if she is pregnant, breast-
777 feeding a baby, or able to get pregnant and not using the required two methods of
778 birth control.
- 779 • The patient confirms that she is not now pregnant, nor will she try to become
780 pregnant during REVLIMID[®] (lenalidomide) therapy, during therapy interruption and
781 for at least 4 weeks after she has completely finished taking REVLIMID[®]
782 (lenalidomide).
- 783 • If the patient is able to become pregnant, she must use at least one highly effective
784 method and one additional effective method of birth control (contraception) AT THE
785 SAME TIME:
- | | | | |
|-----|---|------------|---------------------------------|
| 786 | At least one highly effective method | <u>AND</u> | One additional effective method |
| 787 | IUD | | Latex condom |
| 788 | Hormonal (birth control pills, injections, patch or implants) | | Diaphragm |
| 789 | Tubal ligation | | Cervical cap |
| 790 | Partner's vasectomy | | |
- 791 • These birth control methods must be used for at least 4 weeks before beginning
792 REVLIMID[®] (lenalidomide) therapy, during REVLIMID[®] (lenalidomide) therapy,
793 during therapy interruption and for 4 weeks following discontinuation of
794 REVLIMID[®] (lenalidomide) therapy.
- 795 • The patient must use these birth control methods unless she completely abstains from
796 heterosexual sexual contact.
- 797 • If a hormonal method (birth control pills, injections, patch or implants) or IUD is not
798 medically possible for the patient, she may use another highly effective method or
799 two barrier methods AT THE SAME TIME.
- 800 • The patient must have a pregnancy test done by her doctor within 10-14 days and 24
801 hours before REVLIMID[®] (lenalidomide) therapy, then weekly during the first 4
802 weeks of REVLIMID[®] (lenalidomide) therapy.
- 803 • Thereafter, the patient must have a pregnancy test every 4 weeks if she has regular
804 menstrual cycles, or every 2 weeks if her cycles are irregular while she is taking
805 REVLIMID[®] (lenalidomide).
- 806 • The patient must immediately stop taking REVLIMID[®] (lenalidomide) and inform
807 her doctor:

- 808 ○ If she becomes pregnant while taking the drug
- 809 ○ If she misses her menstrual period, or experiences unusual menstrual
- 810 bleeding
- 811 ○ If she stops using birth control
- 812 ○ If she thinks FOR ANY REASON that she may be pregnant
- 813 ○ The patient understands that if her doctor is not available, she can call 1-
- 814 888-668-2528 for information on emergency contraception

815 **Female Patients Not of Childbearing Potential**

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

825 **Male Patients**

- 826 ● The patient has been told by his doctor that he must NEVER have unprotected
- 827 sexual contact with a female who can become pregnant.
- 828 ● Because it is not known whether REVLIMID[®] (lenalidomide) is present in semen,
- 829 his doctor has explained that he must either completely abstain from sexual
- 830 contact with females who are pregnant or able to become pregnant, or he must use
- 831 a latex condom EVERY TIME he engages in any sexual contact with females
- 832 who are pregnant or may become pregnant while he is taking REVLIMID[®]
- 833 (lenalidomide) and for 4 weeks after he stops taking the drug, even if he has had a
- 834 successful vasectomy.
- 835 ● The patient should inform his doctor:
 - 836 ○ If he has had unprotected sexual contact with a female who can become
 - 837 pregnant
 - 838 ○ If he thinks FOR ANY REASON, that his sexual partner may be pregnant.
 - 839 ○ The patient understands that if his doctor is not available, he can call 1-
 - 840 888-668-2528 for information on emergency contraception.

- 841 • The patient cannot donate semen or sperm while taking REVLIMID[®]
842 (lenalidomide).

843

844 **Information for patients and caregivers:**

845

MEDICATION GUIDE

846

REVLIMID[®] (rev-li-mid)

847

(lenalidomide)

848 Read the Medication Guide that comes with REVLIMID[®] before you start taking it and
849 each time you get a new prescription. There may be new information. This Medication
850 Guide does not take the place of talking to your healthcare provider about your medical
851 condition or your treatment.

852

853 **What is the most important information I should know about REVLIMID[®]?**

- 854 • **REVLIMID[®] is only for patients who understand and agree to all of the**
855 **instructions in the REVASSISTSM program.**

- 856 • **REVLIMID[®] may cause serious side effects including:**

857

1. birth defects

858

2. low white blood cells and platelets

859

3. blood clots in veins and in the lungs

860

- 861 **1. Possible birth defects (deformed babies) or death of an unborn baby.** Female
862 patients who are pregnant or who plan to become pregnant must not take
863 REVLIMID[®].

864 **REVLIMID[®] is similar to the medicine thalidomide (THALOMID[®]).** We know
865 thalidomide causes life-threatening birth defects. REVLIMID[®] has not been tested in
866 pregnant women. REVLIMID[®] has harmed unborn animals in animal testing.

867

Female patients must not get pregnant:

868

- for 4 weeks before starting REVLIMID[®]

869

- while taking REVLIMID[®]

870

- during dose interruptions of REVLIMID[®]

871

- for 4 weeks after stopping REVLIMID[®]

872

It is not known if REVLIMID[®] passes into semen, so:

873

- Male patients, including those who have had a vasectomy, must use a latex

874

condom during any sexual contact with a pregnant female or a female that can

875 become pregnant while taking REVLIMID[®] and for 4 weeks after stopping
876 REVLIMID[®].

877 **If you get pregnant while taking REVLIMID[®], stop taking it right away and call**
878 **your healthcare provider. Female partners of males taking REVLIMID[®] should**
879 **call their healthcare provider right away if they get pregnant.** Healthcare
880 providers and patients should report all cases of pregnancy to:

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

883 **2. Low white blood cells (neutropenia) and low platelets (thrombocytopenia).**

884 REVLIMID[®] causes low white blood cells and low platelets in most patients. You
885 may need a blood transfusion or certain medicines if your blood counts drop too low.
886 If you are being treated for del 5q myelodysplastic syndromes (MDS) your blood
887 counts should be checked weekly during the first 8 weeks of treatment with
888 REVLIMID[®], and at least monthly thereafter. If you are being treated for multiple
889 myeloma, your blood counts should be checked every 2 weeks for the first 12 weeks
890 and then at least monthly thereafter.

891 **3. An increased chance for blood clots in veins and in the lungs.** Call your healthcare
892 provider or get emergency medical care right away if you get the following signs or
893 symptoms:

- 894 • shortness of breath
 - 895 • chest pain
 - 896 • arm or leg swelling
- 897

898 ***What is REVLIMID[®] and what is it used for?***

899 REVLIMID[®] is a medicine taken by mouth to treat certain patients who have
900 myelodysplastic syndromes (MDS). Patients with MDS have bone marrow that does not
901 produce enough mature blood cells. This causes a lack of healthy blood cells that can
902 function properly in the body. There are different types of MDS. REVLIMID[®] is for the
903 type of MDS with a chromosome problem where part of chromosome 5 is missing. This
904 type of MDS is known as deletion 5q MDS. Patients with this type of MDS may have
905 low red blood cell counts that require treatment with blood transfusions.

906 REVLIMID[®] is also used with dexamethasone to treat patients with multiple myeloma
907 who have already had another treatment. Multiple myeloma is a cancer of plasma cells.
908 Plasma cells are found in the bone marrow. Plasma cells produce a protein called
909 antibodies. Some antibodies can attack and kill disease causing germs. Patients with this
910 type of cancer may have low blood cell counts and immune problems giving them a
911 higher chance for getting infections such as pneumonia. The bones can be affected
912 leading to bone pain and breaks (fractures).

913

914 REVLIMID[®] can only be:

- 915 • prescribed by healthcare providers who are registered in the RevAssistSM program
- 916 • dispensed by a pharmacy that is registered in the RevAssistSM program
- 917 • given to patients who are registered in the RevAssistSM program and who agree to do
- 918 everything required in the program

919 REVLIMID[®] has not been studied in children under 18 years of age.

920 **Who should not take REVLIMID[®]?**

921 • **Do not take REVLIMID[®] if you are pregnant, plan to become pregnant, or**
922 **become pregnant during REVLIMID[®] treatment.** REVLIMID[®] may cause birth
923 defects. See “What is the most important information I should know about
924 REVLIMID[®]?”

925 • **Do not take REVLIMID[®] if you are allergic to anything in it.** See the end of this
926 Medication Guide for a complete list of ingredients in REVLIMID[®].

927 ***What should I tell my healthcare provider before taking REVLIMID[®]?***

928 Tell your healthcare provider about all of your medical conditions, including if you:

929 • **are pregnant or breastfeeding.** REVLIMID[®] must not be used by women who are
930 pregnant or breastfeeding.

931 **Tell your healthcare provider about all the medicines you take including**
932 **prescription and non-prescription medicines, vitamins and herbal supplements.** It is
933 possible that REVLIMID[®] and other medicines may affect each other causing serious
934 side effects.

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

937 ***How should I take REVLIMID[®]?***

938 • Take REVLIMID[®] exactly as prescribed. You must also follow all the instructions of
939 the RevAssistSM program. Before prescribing REVLIMID[®], your healthcare provider
940 will:

- 941 • explain the RevAssistSM program to you
- 942 • have you sign the Patient-Physician Agreement Form

943 **You will not be prescribed REVLIMID[®] if you cannot agree to or follow all of the**
944 **instructions of the RevAssistSM program.**

945 You will get no more than a 28-day supply of REVLIMID[®] at one time. This is to make
946 sure you follow the RevAssistSM program.

- 947 • Swallow REVLIMID[®] capsules whole with water once a day. **Do not break, chew,**
948 **or open your capsules.**
- 949 • If you miss a dose of REVLIMID[®], take it as soon as you remember that day. If you
950 miss taking your dose for the entire day, go back to taking your regular dose the next
951 day. Do **not** take 2 doses at the same time.
- 952 • If you take too much REVLIMID[®] or overdose, call your healthcare provider or
953 poison control center right away.
- 954 • You will have regular blood tests during your treatment with REVLIMID[®]. If you are
955 being treated for del 5q myelodysplastic syndromes (MDS) you should have your
956 blood tested every week during your first 8 weeks of treatment, and at least monthly
957 after that. If you are being treated for multiple myeloma, your blood counts should be
958 checked every two weeks for the first 12 weeks and then at least monthly after that.
959 Your healthcare provider may adjust your dose of REVLIMID[®] or interrupt your
960 treatment based on the results of your blood tests and on your general condition.
- 961 • Female patients who can get pregnant will get regular pregnancy testing.
- 962 • get a pregnancy test weekly for 4 weeks.
- 963 • Female patients who can become pregnant must agree to use 2 separate forms of
964 effective birth control at the same time, 4 weeks before, while taking, and for 4 weeks
965 after stopping REVLIMID[®].
- 966 • Male patients, even those who have had a vasectomy, must agree to use a latex
967 condom during sexual contact with a pregnant female or a female who can become
968 pregnant.
- 969 **What should I avoid while taking REVLIMID[®]?**
- 970 • **Do not get pregnant while taking REVLIMID[®]** and for 4 weeks after stopping
971 REVLIMID[®]. See “What is the most important information I should know about
972 REVLIMID[®]?”
- 973 • **Do not breastfeed while taking REVLIMID[®]**. We do not know if REVLIMID[®]
974 passes into your milk and harms your baby.
- 975 • **Do not share REVLIMID[®] with other people.** It may cause birth defects and other
976 serious problems.
- 977 • **Do not give blood** while you take REVLIMID[®] and for 4 weeks after stopping
978 REVLIMID[®]. If someone who is pregnant gets your donated blood, her baby may be
979 exposed to REVLIMID[®] and may be born with birth defects.

- 980 • **Male patients should not donate sperm** while taking REVLIMID[®] and for 4 weeks
981 after stopping REVLIMID[®]. If a female who is trying to become pregnant gets your
982 sperm, her baby may be exposed to REVLIMID[®] and may be born with birth defects.

983

984 **What are the possible side effects of REVLIMID[®]?**

- 985 • **REVLIMID[®] may cause serious side effects including:**

- 986 • birth defects
987 • low white blood cells and platelets
988 • blood clots in veins and in the lungs

989 See “What is the most important information I should know about REVLIMID[®]?”

990 Other common side effects of REVLIMID[®] are:

- 991 • diarrhea
992 • itching
993 • rash
994 • tiredness

995 Tell your healthcare provider about any side effect that bothers you or that does not go
996 away.

997 These are not all the side effects with REVLIMID[®]. Ask your healthcare provider or
998 pharmacist for more information.

999 **How should I store REVLIMID[®]?**

1000 Store REVLIMID[®] at room temperature, 59° to 86°F (15° to 30° C).

1001 **Keep REVLIMID[®] and all medicines out of the reach of children.**

1002 ***General information about the safe and effective use of REVLIMID[®]***

1003 Medicines are sometimes prescribed for conditions that are not mentioned in Medication
1004 Guides. **Do not** take REVLIMID[®] for conditions for which it was not prescribed. **Do not**
1005 give REVLIMID[®] to other people, even if they have the same symptoms you have. It
1006 may harm them.

1007 This Medication Guide provides a summary of the most important information about
1008 REVLIMID[®]. If you would like more information, talk with your healthcare provider.
1009 You can ask your healthcare provider or pharmacist for information about REVLIMID[®]
1010 that is written for health professionals. You can also call 1-888-423-5436 or visit
1011 www.REVLIMID.com.

1012 ***What are the ingredients in REVLIMID[®]?***


- 1013 REVLIMID[®] (lenalidomide) capsules contain 5 mg, 10 mg, 15mg or 25 mg of
1014 lenalidomide and are available as gelatin capsules for oral administration.
- 1015 The inactive ingredients of REVLIMID[®] capsules are: lactose anhydrous,
1016 microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.
- 1017 The 5 mg and 25 mg capsule shells contain gelatin, titanium dioxide and black ink. The
1018 10 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide
1019 and black ink. The 15 mg capsule shell contains gelatin, FD&C blue #2, titanium dioxide
1020 and black ink.
- 1021 Manufactured for Celgene Corporation
- 1022 Summit, NJ 07901
- 1023 This Medication Guide has been approved by the US Food and Drug Administration.

59572-405-30

59572-405-30

OSG00495

NDC 59572-405-30


Revlimid[®]
(lenalidomide) capsules

5 mg

WARNING: POTENTIAL FOR HUMAN BIRTH DEFECTS.


Rx only 30 Capsules

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).

Manufactured for
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

See prescribing information for dosing and administration.

12/05 BT40530.002


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This label may not be the latest approved by FDA.
For current labeling information, please visit <https://www.fda.gov/drugsatfda>


NDC 59572-405-00

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).


Manufactured for
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

See prescribing information for dosing and administration.

12/05 BT40500.002




59572-405-00



Revlimid[®]
(lenalidomide) capsules

5 mg

WARNING: POTENTIAL FOR HUMAN BIRTH DEFECTS.



© 2005 Celgene Corporation

OSG00496

Rx only **100 Capsules**

This label may not be the latest approved by FDA.
For current labeling information, please visit <https://www.fda.gov/drugsatfda>



OSG00497

NDC 59572-410-30


Revlimid[®]
(lenalidomide) capsules

10 mg

WARNING: POTENTIAL FOR HUMAN
BIRTH DEFECTS.

Rx only 30 Capsules

Store at 25°C (77°F); excursions
permitted to 15–30°C (59–86°F).

Manufactured for
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

See prescribing information for
dosing and administration.

12/05 BT41030.002



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This label may not be the latest approved by FDA.
For current labeling information, please visit <https://www.fda.gov/drugsatfda>

NDC 59572-410-00

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).

Manufactured for
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

See prescribing information for
dosing and administration.

12/05 BT41000.002



Revlimid[®]
(lenalidomide) capsules

10 mg

**WARNING: POTENTIAL FOR HUMAN
BIRTH DEFECTS.**

OSG00498

Rx only 100 Capsules



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FPO

NDC 59572-XXX-XX

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).

Manufactured for
Celgene Corporation
85 Morris Avenue
Summit, NJ 07901

See prescribing information for
dosing and administration.

10/05 BTXXXXX.001




Revlimid[®]
(lenalidomide) capsules

15 mg

WARNING: POTENTIAL FOR HUMAN
BIRTH DEFECTS.

Rx only 21 Capsules



© 2005 Celgene Corporation

 **FPO**

NDC 59572-XXX-XX


Revlimid[®]
(lenalidomide) capsules

15 mg

WARNING: POTENTIAL FOR HUMAN BIRTH DEFECTS.

Rx only 100 Capsules

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).

Manufactured for
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

See prescribing information for dosing and administration.

10/05 BTXXXXX.001


© 2005 Celgene Corporation

FPO


NDC 59572-XXX-XX

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).

Manufactured for
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

See prescribing information for
dosing and administration.

10/05 BTXXXXX.001



Revlimid[®]
(lenalidomide) capsules

25 mg

WARNING: POTENTIAL FOR HUMAN
BIRTH DEFECTS.

Rx only 25 Capsules



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 **FPO**

NDC 59572-XXX-XX

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).

Manufactured for
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

See prescribing information for dosing and administration.

10/05 BTXXXXX.001


Revlimid[®]
(lenalidomide) capsules

25 mg

WARNING: POTENTIAL FOR HUMAN BIRTH DEFECTS.

Rx only 100 Capsules


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