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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 "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.

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 RevAssist[®]
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 RevAssist[®] 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 materials 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% of**
126 **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.**

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

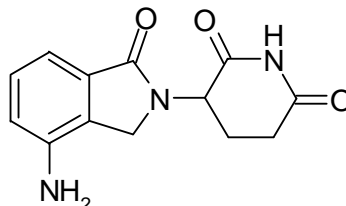
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146 **DESCRIPTION**

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

151

Chemical Structure of Lenalidomide



152

153 3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

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

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

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

169 **CLINICAL PHARMACOLOGY**

170 **Mechanism of Action**

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

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

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

185 **Pharmacokinetics and Drug Metabolism**

186 ***Absorption:***

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

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

199 **Pharmacokinetic Parameters**

200 ***Distribution:***

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

202 ***Metabolism and Excretion:***

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

207 ***Special Populations:***

208 *Patients with Renal Insufficiency:* The pharmacokinetics of lenalidomide were studied in
209 patients with renal impairment due to nonmalignant conditions. In this study, 5 patients
210 with mild renal function impairment (creatinine clearance 57-74 mL/min), 6 patients with
211 moderate renal function impairment (creatinine clearance 33-46 mL/min), 6 patients with
212 severe renal function impairment (creatinine clearance 17-29 mL/min), and 6 patients
213 with end stage renal disease requiring dialysis were administered a single oral 25-mg
214 dose of REVLIMID[®] (lenalidomide). As a control group comparator, 7 healthy subjects
215 of similar age with normal renal function (creatinine clearance 83-145 mL/min) were also
216 administered a single oral 25-mg dose of REVLIMID[®] (lenalidomide). As creatinine

217 clearance decreased from mild to severe impairment, half-life increased and drug
218 clearance decreased linearly. Patients with moderate and severe renal impairment had a
219 3-fold increase in half-life and a 66% to 75% decrease in drug clearance compared to
220 healthy subjects. Patients on hemodialysis (n=6) given a single, 25-mg dose of
221 lenalidomide had an approximate 4.5-fold increase in half-life and an 80% decrease in
222 drug clearance compared to healthy subjects. Approximately 40% of the administered
223 dose was removed from the body during a single dialysis session.

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

227 In multiple myeloma patients, those patients with mild renal impairment had an AUC
228 56% greater than those with normal renal function.

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

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

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

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

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

236 **CLINICAL STUDIES**

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

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

245 This major study enrolled 148 patients who had RBC transfusion dependent anemia.
246 RBC-transfusion dependence was defined as having received ≥ 2 units of RBCs within 8
247 weeks prior to study treatment. The study enrolled patients with absolute neutrophil
248 counts (ANC) $\geq 500/\text{mm}^3$, platelet counts $\geq 50,000/\text{mm}^3$, serum creatinine ≤ 2.5 mg/dL,
249 serum SGOT/AST or SGPT/ALT ≤ 3.0 x upper limit of normal (ULN), and serum direct
250 bilirubin ≤ 2.0 mg/dL. Granulocyte colony-stimulating factor was permitted for patients
251 who developed neutropenia or fever in association with neutropenia. Baseline patient and
252 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.

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

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

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

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

265 The dose of REVLIMID[®] (lenalidomide) was reduced or interrupted at least once due to
266 an adverse event in 118 (79.7%) of the 148 patients; the median time to the first dose
267 reduction or interruption was 21 days (mean, 35.1 days; range, 2-253 days), and the
268 median duration of the first dose interruption was 22 days (mean, 28.5 days; range, 2-265
269 days). A second dose reduction or interruption due to adverse events was required in 50
270 (33.8%) of the 148 patients. The median interval between the first and second dose

271 reduction or interruption was 51 days (mean, 59.7 days; range, 15-205 days) and the
272 median duration of the second dose interruption was 21 days (mean, 26 days; range, 2-
273 148 days).

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

276 **Multiple Myeloma**

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

282 In both studies, patients in the REVLIMID[®] (lenalidomide)/dexamethasone group took
283 25 mg of REVLIMID[®] (lenalidomide) orally once daily on Days 1 to 21 and a matching
284 placebo capsule once daily on Days 22 to 28 of each 28-day cycle. Patients in the
285 placebo/dexamethasone group took 1 placebo capsule on Days 1 to 28 of each 28-day
286 cycle. Patients in both treatment groups took 40 mg of dexamethasone orally once daily
287 on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy.

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

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

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

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299
300

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% |

301

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

305
306 Preplanned interim analyses of both studies showed that the combination of REVLIMID[®]
307 (lenalidomide)/dexamethasone was significantly superior to dexamethasone alone for
308 TTP. The studies were unblinded to allow patients in the placebo/dexamethasone group
309 to receive treatment with the REVLIMID[®] (lenalidomide)/dexamethasone combination.

310
311 Table 3 summarizes TTP and response rates based on the best response assessments for
312 Studies 1 and 2.

313
314

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] | |

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¹ NE, Not estimable due to short follow-up.

² Hazard Ratio of Revlimid/Dexamethasone to Placebo/Dexamethasone

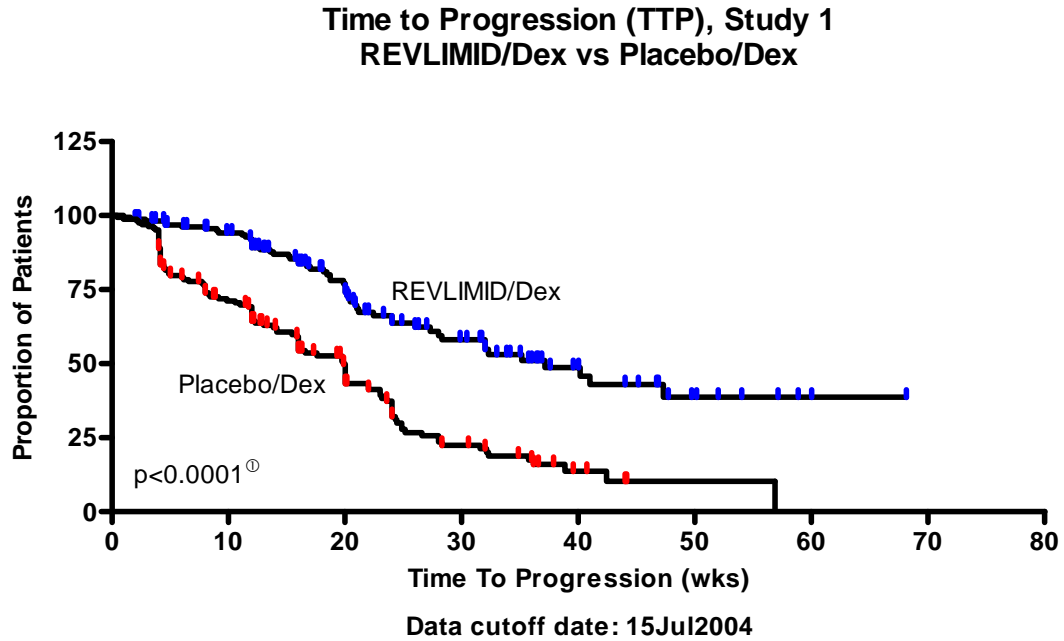
³ The p-value is based on a one-tailed unstratified log rank test.

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

322

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

324



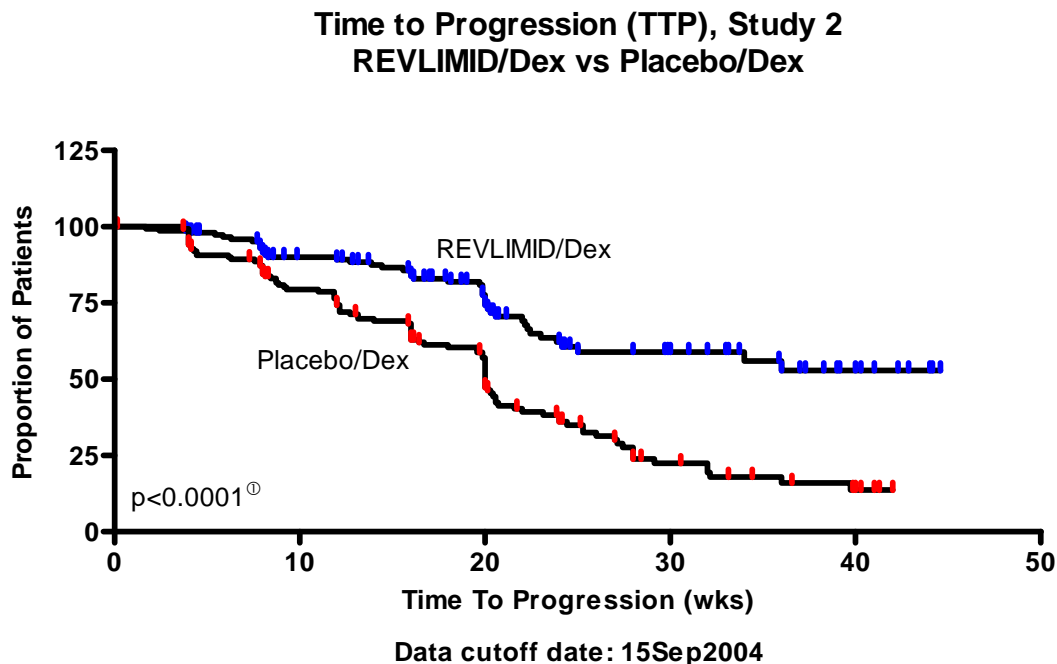
^⓪ p-value from log-rank test

325

326

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

328 **Figure 2: Kaplan-Meier Estimate of Time to Progression — Study 2**
329



[Ⓛ] p-value from log-rank test

330
331 The median duration of Study 2 follow-up was 22.3 weeks.

332 **INDICATIONS AND USAGE**

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

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

339 **CONTRAINDICATIONS**

340 **Pregnancy Category X: (See BOXED WARNINGS)**

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

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

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

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

369 **WARNINGS**

370 **Pregnancy Category X: (See BOXED WARNINGS and CONTRAINDICATIONS)**

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

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

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

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

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

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

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

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

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

403 **Eighty percent of patients with del 5q MDS had to have a dose delay or reduction**
404 **during the major study for the indication. Thirty-four percent of patients had to**
405 **have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in**
406 **80% of patients enrolled in the study. In the 48% of patients who developed Grade**
407 **3 or 4 neutropenia, the median time to onset was 42 days (range, 14-411 days), and**
408 **the median time to documented recovery was 17 days (range, 2-170 days). In the**
409 **54% of patients who developed Grade 3 or 4 thrombocytopenia, the median time to**
410 **onset was 28 days (range, 8-290 days), and the median time to documented recovery**
411 **was 22 days (range, 5-224 days). Patients on therapy for del 5q myelodysplastic**
412 **syndromes should have their complete blood counts monitored weekly for the first 8**
413 **weeks of therapy and at least monthly thereafter. Patients may require dose**
414 **interruption and/or reduction. Patients may require use of blood product support**
415 **and/or growth factors. (See DOSAGE AND ADMINISTRATION)**

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

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

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

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

434

435 PRECAUTIONS

436 Angioedema, Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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

444 Tumor Lysis Syndrome

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

449 Information for Patients

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

461 Laboratory Tests

462 The MDS clinical study enrolled patients with absolute neutrophil counts (ANC) \geq
463 $500/\text{mm}^3$, platelet counts $\geq 50,000/\text{mm}^3$, serum creatinine ≤ 2.5 mg/dL, serum
464 SGOT/AST or SGPT/ALT ≤ 3.0 x upper limit of normal (ULN), and serum direct
465 bilirubin ≤ 2.0 mg/dL. A complete blood cell count (CBC), including white blood cell
466 count with differential, platelet count, hemoglobin, and hematocrit should be performed
467 weekly for the first 8 weeks of REVLIMID[®] (lenalidomide) treatment and monthly
468 thereafter to monitor for cytopenias.

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

474 **Drug Interactions**

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

479 Co-administration of multiple doses of 10 mg of lenalidomide had no effect on the single
480 dose pharmacokinetics of R- and S-warfarin. Co-administration of single 25-mg dose
481 warfarin had no effect on the pharmacokinetics of total lenalidomide. Expected changes
482 in laboratory assessments of PT and INR were observed after warfarin administration, but
483 these changes were not affected by concomitant lenalidomide administration.

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

489 **Carcinogenesis, mutagenesis, impairment of fertility**

490 *Carcinogenicity:* Carcinogenicity studies with lenalidomide have not been conducted.

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

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

500 **Pregnancy**

501 **Pregnancy Category X: (See BOXED WARNINGS and CONTRAINDICATIONS)**

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

515 **Use in Nursing Mothers**

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

520 **Pediatric Use**

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

523 **Geriatric Use**

524 REVLIMID[®] (lenalidomide) has been used in del 5q MDS clinical trials in patients up to
525 95 years of age.

526 Of the 148 patients with del 5q MDS enrolled in the major study, 38% were age 65 and
527 over, while 33% were age 75 and over. Although the overall frequency of adverse events
528 (100%) was the same in patients over 65 years of age as in younger patients, the
529 frequency of serious adverse events was higher in patients over 65 years of age than in
530 younger patients (54% vs. 33%). A greater proportion of patients over 65 years of age
531 discontinued from the clinical studies because of adverse events than the proportion of
532 younger patients (27% vs. 16%). No differences in efficacy were observed between
533 patients over 65 years of age and younger patients.

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

536

537 Of the 692 MM patients enrolled in Studies 1 and 2, 45% were age 65 or over while 12%
538 of patients were age 75 and over. The percentage of patients age 65 or over was not
539 significantly different between the REVLIMID[®] (lenalidomide)/dexamethasone and
540 placebo/dexamethasone groups. Of the 346 patients who received REVLIMID[®]
541 (lenalidomide)/dexamethasone, 46% were age 65 and over. In both studies, patients > 65
542 years of age were more likely than patients ≤ 65 years of age to experience diarrhea,
543 fatigue, pulmonary embolism, and syncope following use of REVLIMID[®]
544 (lenalidomide). No differences in efficacy were observed between patients over 65 years
545 of age and younger patients.
546

547

548 **Renal Impairment**

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

553 **ADVERSE REACTIONS**

554 **Myelodysplastic Syndromes**

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

561 Thrombocytopenia (61.5%; 91/148) and neutropenia (58.8%; 87/148) were the most
562 frequently reported adverse events observed. The next most common adverse events
563 observed were diarrhea (48.6%; 72/148), pruritus (41.9%; 62/148), rash (35.8%; 53/148)
564 and fatigue (31.1%; 46/148). Table 4 summarizes the adverse events that were reported in
565 ≥ 5% of the REVLIMID[®] (lenalidomide) treated patients in the del 5q MDS clinical
566 study. Table 5 summarizes the most frequently observed Grade 3 and Grade 4 adverse
567 reactions regardless of relationship to treatment with REVLIMID[®] (lenalidomide). In the
568 single-arm studies conducted, it is often not possible to distinguish adverse events that are
569 drug-related and those that reflect the patient’s underlying disease.

570 **Table 4: Summary of Adverse Events Reported in ≥5% of the**
571 **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 $\geq 1\%$ 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.

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

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

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

- 583 infarction, myocardial ischemia, atrial fibrillation aggravated, bradycardia NOS,
584 cardiogenic shock, pulmonary edema NOS, supraventricular arrhythmia NOS,
585 tachyarrhythmia, ventricular dysfunction
- 586 **Ear and labyrinth disorders:** vertigo
- 587 **Endocrine disorders:** Basedow's disease
- 588 **Gastrointestinal disorders:** gastrointestinal hemorrhage NOS, colitis ischemic,
589 intestinal perforation NOS, rectal hemorrhage, colonic polyp, diverticulitis NOS,
590 dysphagia, gastritis NOS, gastroenteritis NOS, gastroesophageal reflux disease,
591 obstructive inguinal hernia, irritable bowel syndrome, melena, pancreatitis due to biliary
592 obstruction, pancreatitis NOS, perirectal abscess, small intestinal obstruction NOS, upper
593 gastrointestinal hemorrhage
- 594 **General disorders and administration site conditions:** disease progression NOS, fall,
595 gait abnormal, intermittent pyrexia, nodule, rigors, sudden death
- 596 **Hepatobiliary disorders:** hyperbilirubinemia, cholecystitis acute NOS, cholecystitis
597 NOS, hepatic failure
- 598 **Immune system disorders:** hypersensitivity NOS
- 599 **Infections and infestations:** infection NOS, bacteremia, central line infection, clostridial
600 infection NOS, ear infection NOS, *Enterobacter* sepsis, fungal infection NOS, herpes
601 viral infection NOS, influenza, kidney infection NOS, *Klebsiella* sepsis, lobar pneumonia
602 NOS, localized infection, oral infection, *Pseudomonas* infection NOS, septic shock,
603 sinusitis acute NOS, sinusitis NOS, *Staphylococcal* infection, urosepsis
- 604 **Injury, poisoning and procedural complications:** femur fracture, transfusion reaction,
605 cervical vertebral fracture, femoral neck fracture, fractured pelvis NOS, hip fracture,
606 overdose NOS, post procedural hemorrhage, rib fracture, road traffic accident, spinal
607 compression fracture
- 608 **Investigations:** blood creatinine increased, culture NOS negative, hemoglobin decreased,
609 liver function tests NOS abnormal, troponin I increased
- 610 **Metabolism and nutrition disorders:** dehydration, gout, hypernatremia, hypoglycemia
611 NOS
- 612 **Musculoskeletal and connective tissue disorders:** arthritis NOS, arthritis NOS
613 aggravated, gouty arthritis, neck pain, chondrocalcinosis pyrophosphate
- 614 **Neoplasms benign, malignant and unspecified:** acute leukemia NOS, acute myeloid
615 leukemia NOS, bronchoalveolar carcinoma, lung cancer metastatic, lymphoma NOS,
616 prostate cancer metastatic

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

620 **Psychiatric disorders:** confusional state

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

623 **Reproductive system and breast disorders:** pelvic pain NOS

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

627 **Skin and subcutaneous tissue disorders:** acute febrile neutrophilic dermatosis

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

630

631 **Multiple Myeloma**

632 Data were evaluated from 691 patients in two studies who received at least one dose of
633 REVLIMID[®] (lenalidomide)/dexamethasone (346 patients) or placebo/dexamethasone
634 (345 patients).

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

644

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

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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 | 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) |

651

^a See WARNINGS

652

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

655

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

| 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) |
| 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) |

658 ^a See WARNINGS

659 **Thrombotic Events (See WARNINGS)**

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

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

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

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

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

672 **Eye disorders:** blindness

673 **Gastrointestinal disorders:** abdominal pain NOS, colitis pseudomembranous, gastritis
674 NOS, gastrointestinal hemorrhage NOS, peptic ulcer hemorrhage, upper gastrointestinal
675 hemorrhage

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

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

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

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

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

690 **Musculoskeletal and connective tissue disorders:** myopathy steroid, back pain,
691 myopathy

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

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

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

700 **Respiratory, thoracic and mediastinal disorders:** bronchopneumopathy, hypoxia

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

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

705 **OVERDOSAGE**

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

707 **DOSAGE AND ADMINISTRATION**

708 **Myelodysplastic Syndromes**

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

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

716 **Dose Adjustments During Treatment**

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

719 **Platelet counts**

720 **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 |

721

722 **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 |

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

725 **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 |

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

728 **Neutrophil counts (ANC)⁺**

729 **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 |

730

731 **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 |

732 Patients who experience neutropenia at 5 mg daily should have their dosage adjusted as
733 follows:

734 **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 |

735

736

⁺ Absolute neutrophil count

737 **Multiple Myeloma**

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

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

746 **Dose Adjustments During Treatment**

747 Dose modification guidelines, as summarized below are recommended to manage Grade
748 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicity judged to be
749 related to lenalidomide.

750 **Platelet counts**

751 **Thrombocytopenia**

| When Platelets | Recommended Course |
|---------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Fall to <30,000/mcL | Interrupt REVLIMID [®] treatment, follow CBC weekly |
| Return to $\geq 30,000/mcL$ | Restart REVLIMID [®] at 15 mg daily |
| For each subsequent drop <30,000/mcL Return to $\geq 30,000/mcL$ | Interrupt REVLIMID [®] treatment Resume REVLIMID [®] at 5 mg less than the previous dose. Do not dose below 5 mg daily |

752 **Neutrophil counts (ANC)**

753 **Neutropenia**

| When Neutrophils | Recommended Course |
|-------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Fall to <1000/mcL | Interrupt REVLIMID [®] treatment, add G-CSF, follow CBC weekly |
| Return to $\geq 1,000/mcL$ and neutropenia is the only toxicity | Resume REVLIMID [®] at 25 mg daily |
| Return to $\geq 1,000/mcL$ 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 |

754

755 **Starting Dose Adjustment for Renal Impairment:**

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

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

765
766
767

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 |

768
769
770
771
772

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.

773

Other Grade 3/4 Toxicities

774
775

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.

776

HOW SUPPLIED

777
778

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

779

REVLIMID[®] (lenalidomide) is supplied as:

780
781

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

782

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

- 783 5 mg bottles of 100 (NDC 59572-405-00)
- 784 Blue/green and pale yellow opaque capsules imprinted “REV” on one half and “10 mg”
785 on the other half in black ink:
- 786 10 mg bottles of 28 (NDC 59572-410-28)
- 787 10 mg bottles of 100 (NDC 59572-410-00)
- 788 Powder blue and white opaque capsules imprinted “REV” on one half and “15 mg” on
789 the other half in black ink:
- 790 15 mg bottles of 21 (NDC 59572-415-21)
- 791 15 mg bottles of 100 (NDC 59572-415-00)
- 792 White opaque capsules imprinted “REV” on one half and “25 mg” on the other half in
793 black ink:
- 794 25 mg bottles of 21 (NDC 59572-425-21)
- 795 25 mg bottles of 100 (NDC 59572-425-00)

796 **Storage and Dispensing**

- 797 Dispense no more than a 28-day supply.
- 798 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled
799 Room Temperature].
- 800 Rx only.
- 801 Manufactured for Celgene Corporation
- 802 86 Morris Avenue
- 803 Summit, NJ 07901

804 **Important Information and WARNINGS for All Patients Taking**

805 **REVLIMID[®] (lenalidomide)**

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

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

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

847 • These birth control methods must be used for at least 4 weeks before beginning
848 REVLIMID[®] (lenalidomide) therapy, during REVLIMID[®] (lenalidomide) therapy,
849 during therapy interruption and for 4 weeks following discontinuation of
850 REVLIMID[®] (lenalidomide) therapy.

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

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

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

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

862 • The patient must immediately stop taking REVLIMID[®] (lenalidomide) and inform
863 her doctor:

864 ○ If she becomes pregnant while taking the drug.

865 ○ If she misses her menstrual period, or experiences unusual menstrual
866 bleeding.

867 ○ If she stops using birth control.

868 ○ If she thinks FOR ANY REASON that she may be pregnant.

869 ○ The patient understands that if her doctor is not available, she can call
870 1-888-668-2528 for information on emergency contraception.

871 **Female Patients Not of Childbearing Potential**

872 • The patient certifies that she is not now pregnant, nor of childbearing potential as
873 she has been postmenopausal naturally for at least 24 months (been through the
874 change of life); or she has had a hysterectomy or bilateral oophorectomy.

875 • The patient or guardian certifies that a prepubertal female child is not now
876 pregnant, nor is of childbearing potential as menstruation has not yet begun,
877 and/or the child will not be engaging in heterosexual sexual contact for at least 4
878 weeks before REVLIMID[®] (lenalidomide) therapy, during REVLIMID[®]

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

881 **Male Patients**

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

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

891 • The patient should inform his doctor:

892 ○ If he has had unprotected sexual contact with a female who can become
893 pregnant.

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

895 ○ The patient understands that if his doctor is not available, he can call
896 1-888-668-2528 for information on emergency contraception.

897 • The patient cannot donate semen or sperm while taking REVLIMID[®]
898 (lenalidomide).

899

900

901

RevPlyPI.006/MG.006 12/08

902 **Information for patients and caregivers:**

903

904

MEDICATION GUIDE

905

REVLIMID[®] (rev-li-mid)

906

(lenalidomide)

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

911

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

913 • **REVLIMID[®] is only for patients who understand and agree to all of the**
914 **instructions in the RevAssist[®] program.**

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

916

1. birth defects

917

2. low white blood cells and platelets

918

3. blood clots in veins and in the lungs

919

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

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

926 **Female patients must not get pregnant:**

927

• for 4 weeks before starting REVLIMID[®]

928

• while taking REVLIMID[®]

929

• during dose interruptions of REVLIMID[®]

930

• for 4 weeks after stopping REVLIMID[®]

931

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

932

• Male patients, including those who have had a vasectomy, must use a latex
933 condom during any sexual contact with a pregnant female or a female that can
934 become pregnant while taking REVLIMID[®] and for 4 weeks after stopping
935 REVLIMID[®].

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

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

942 **2. Low white blood cells (neutropenia) and low platelets (thrombocytopenia).**
943 REVLIMID[®] causes low white blood cells and low platelets in most patients. You
944 may need a blood transfusion or certain medicines if your blood counts drop too low.
945 If you are being treated for del 5q myelodysplastic syndromes (MDS) your blood
946 counts should be checked weekly during the first 8 weeks of treatment with
947 REVLIMID[®], and at least monthly thereafter. If you are being treated for multiple
948 myeloma, your blood counts should be checked every 2 weeks for the first 12 weeks
949 and then at least monthly thereafter.

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

- 953 • shortness of breath
 - 954 • chest pain
 - 955 • arm or leg swelling
- 956

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

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

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

972

973 REVLIMID[®] can only be:

- 974 • prescribed by healthcare providers who are registered in the RevAssist[®] program

- 975 • dispensed by a pharmacy that is registered in the RevAssist[®] program
976 • given to patients who are registered in the RevAssist[®] program and who agree to do
977 everything required in the program

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

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

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

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

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

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

- 988 • **are pregnant or breastfeeding.** REVLIMID[®] must not be used by women who are
989 pregnant or breastfeeding.

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

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

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

- 997 • Take REVLIMID[®] exactly as prescribed. You must also follow all the instructions of
998 the RevAssist[®] program. Before prescribing REVLIMID[®], your healthcare provider
999 will:

- 1000 • explain the RevAssist[®] program to you
1001 • have you sign the Patient-Physician Agreement Form

1002 **You will not be prescribed REVLIMID[®] if you cannot agree to or follow all of the**
1003 **instructions of the RevAssist[®] program.**

1004 You will get no more than a 28-day supply of REVLIMID[®] at one time. This is to make
1005 sure you follow the RevAssist[®] program.

- 1006 • Swallow REVLIMID[®] capsules whole with water once a day. **Do not break, chew,**
1007 **or open your capsules.**

- 1008 • If you miss a dose of REVLIMID[®], take it as soon as you remember that day. If you
1009 miss taking your dose for the entire day, go back to taking your regular dose the next
1010 day. Do **not** take 2 doses at the same time.
- 1011 • If you take too much REVLIMID[®] or overdose, call your healthcare provider or
1012 poison control center right away.
- 1013 • You will have regular blood tests during your treatment with REVLIMID[®]. If you are
1014 being treated for del 5q myelodysplastic syndromes (MDS) you should have your
1015 blood tested every week during your first 8 weeks of treatment, and at least monthly
1016 after that. If you are being treated for multiple myeloma, your blood counts should be
1017 checked every two weeks for the first 12 weeks and then at least monthly after that.
1018 Your healthcare provider may adjust your dose of REVLIMID[®] or interrupt your
1019 treatment based on the results of your blood tests and on your general condition.
- 1020 • Female patients who can get pregnant will get regular pregnancy testing.
- 1021 • get a pregnancy test weekly for 4 weeks.
- 1022 • Female patients who can become pregnant must agree to use 2 separate forms of
1023 effective birth control at the same time, 4 weeks before, while taking, and for 4 weeks
1024 after stopping REVLIMID[®].
- 1025 • Male patients, even those who have had a vasectomy, must agree to use a latex
1026 condom during sexual contact with a pregnant female or a female who can become
1027 pregnant.
- 1028 **What should I avoid while taking REVLIMID[®]?**
- 1029 • **Do not get pregnant while taking REVLIMID[®]** and for 4 weeks after stopping
1030 REVLIMID[®]. See “What is the most important information I should know about
1031 REVLIMID[®]?”
- 1032 • **Do not breastfeed while taking REVLIMID[®]**. We do not know if REVLIMID[®]
1033 passes into your milk and harms your baby.
- 1034 • **Do not share REVLIMID[®] with other people.** It may cause birth defects and other
1035 serious problems.
- 1036 • **Do not give blood** while you take REVLIMID[®] and for 4 weeks after stopping
1037 REVLIMID[®]. If someone who is pregnant gets your donated blood, her baby may be
1038 exposed to REVLIMID[®] and may be born with birth defects.
- 1039 • **Male patients should not donate sperm** while taking REVLIMID[®] and for 4 weeks
1040 after stopping REVLIMID[®]. If a female who is trying to become pregnant gets your
1041 sperm, her baby may be exposed to REVLIMID[®] and may be born with birth defects.
- 1042

1043 **What are the possible side effects of REVLIMID[®]?**

1044 • **REVLIMID[®] may cause serious side effects including:**

- 1045 • birth defects
- 1046 • low white blood cells and platelets
- 1047 • blood clots in veins and in the lungs

1048 See “What is the most important information I should know about REVLIMID[®]?”

1049 Other common side effects of REVLIMID[®] are:

- 1050 • diarrhea
- 1051 • itching
- 1052 • rash
- 1053 • tiredness

1054 Tell your healthcare provider about any side effect that bothers you or that does not go
1055 away.

1056 These are not all the side effects with REVLIMID[®]. Ask your healthcare provider or
1057 pharmacist for more information.

1058 **How should I store REVLIMID[®]?**

1059 Store REVLIMID[®] at room temperature, 59° to 86°F (15° to 30°C).

1060 **Keep REVLIMID[®] and all medicines out of the reach of children.**

1061 ***General information about the safe and effective use of REVLIMID[®]***

1062 Medicines are sometimes prescribed for conditions that are not mentioned in Medication
1063 Guides. **Do not** take REVLIMID[®] for conditions for which it was not prescribed. **Do not**
1064 give REVLIMID[®] to other people, even if they have the same symptoms you have. It
1065 may harm them.

1066 This Medication Guide provides a summary of the most important information about
1067 REVLIMID[®]. If you would like more information, talk with your healthcare provider.
1068 You can ask your healthcare provider or pharmacist for information about REVLIMID[®]
1069 that is written for healthcare professionals. You can also call 1-888-423-5436 or visit
1070 www.REVLIMID.com.

1071 ***What are the ingredients in REVLIMID[®]?***

1072 REVLIMID[®] (lenalidomide) capsules contain 5 mg, 10 mg, 15 mg or 25 mg of
1073 lenalidomide and are available as gelatin capsules for oral administration.

1074 The inactive ingredients of REVLIMID[®] capsules are: lactose anhydrous,
1075 microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

1076 The 5 mg and 25 mg capsule shells contain gelatin, titanium dioxide and black ink. The
1077 10 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide
1078 and black ink. The 15 mg capsule shell contains gelatin, FD&C blue #2, titanium dioxide
1079 and black ink.

1080 Manufactured for Celgene Corporation

1081 Summit, NJ 07901

1082 This Medication Guide has been approved by the US Food and Drug Administration.

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