

1 **REVLIMID[®] (lenalidomide)**

2 5 mg, 10 mg, 15 mg and 25 mg capsules

3 **WARNINGS:**

- 4 1. **POTENTIAL FOR HUMAN BIRTH DEFECTS**
5 2. **HEMATOLOGIC TOXICITY (NEUTROPENIA AND**
6 **THROMBOCYTOPENIA)**
7 3. **DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM**
8

9 **POTENTIAL FOR HUMAN BIRTH DEFECTS**

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

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

17 **Special Prescribing Requirements**

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

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

30 **RevAssist[®] PROGRAM DESCRIPTION**

31 **Prescribers**

32 REVLIMID[®] (lenalidomide) can be prescribed only by licensed prescribers who are
33 registered in the RevAssist[®] program and understand the potential risk of teratogenicity if
34 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.**

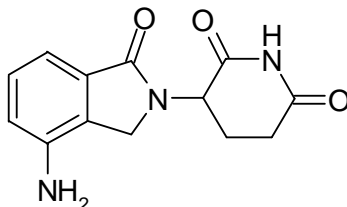
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146 **DESCRIPTION**

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

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