

**REVLIMID<sup>®</sup> (lenalidomide)**

5 mg & 10 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<sup>®</sup> (lenalidomide).**

**Special Prescribing Requirements**

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

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

**CELGENE'S REVASSIST<sup>SM</sup> PROGRAM DESCRIPTION**

**Prescribers**

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

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

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

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

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

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

67 If pregnancy does occur during REVLIMID<sup>®</sup> (lenalidomide) treatment, REVLIMID<sup>®</sup>  
68 (lenalidomide) must be discontinued immediately.

69 Any suspected fetal exposure to REVLIMID<sup>®</sup> (lenalidomide) should be reported to the  
70 FDA *via* the MedWatch number at 1-800-FDA-1088 and also to Celgene Corporation at  
71 1-888-4CELGEN. The patient should be referred to an obstetrician/gynecologist  
72 experienced in reproductive toxicity for further evaluation and counseling.

73 **Female Patients**

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

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

98 **Male Patients**

99 REVLIMID<sup>®</sup> (lenalidomide) should be used in sexually active males when the PATIENT  
100 MEETS ALL OF THE FOLLOWING CONDITIONS:

- 101 • he appears to understand the risks associated with the drug and is thought to be able  
102 to reliably carry out instructions.
- 103 • he is capable of complying with the contraceptive measures that are appropriate for  
104 men, patient registration, and patient survey as described in the RevAssist<sup>SM</sup> program.
- 105 • he has received both oral and written warnings of the potential risks of taking  
106 lenalidomide and exposing a fetus to the drug.

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

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

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

129 **DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM**

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

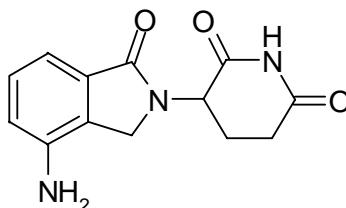
141 **You can get the information about REVLIMID® and the RevAssist<sup>SM</sup> program on**  
142 **the internet at [www.REVLIMID.com](http://www.REVLIMID.com) or by calling the manufacturer's toll free**  
143 **number 1-888-4CELGEN.**

144 **DESCRIPTION**

145 REVLIMID<sup>®</sup> (lenalidomide), a thalidomide analogue, is an immunomodulatory agent  
146 with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -  
147 2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:

148

### Chemical Structure of Lenalidomide



149

150 3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

151 The empirical formula for lenalidomide is C<sub>13</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub>, and the gram molecular weight is  
152 259.3.

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

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

## 165 CLINICAL PHARMACOLOGY

### 166 Mechanism of Action:

167 The mechanism of action of lenalidomide remains to be fully characterized.  
168 Lenalidomide possesses immunomodulatory and antiangiogenic properties.  
169 Lenalidomide inhibited the secretion of pro-inflammatory cytokines and increased the  
170 secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells.  
171 Lenalidomide inhibited cell proliferation with varying effectiveness (IC<sub>50</sub>s) in some but  
172 not all cell lines. Of cell lines tested, lenalidomide was effective in inhibiting growth of  
173 Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5)  
174 but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell  
175 line, also with a deletion of one chromosome 5) and other cell lines without chromosome  
176 5 deletions. Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not  
177 COX-1 in vitro.

### 178 Pharmacokinetics and Drug Metabolism:

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