Revlimid® (lenalidomide) capsules

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REVLIMID is NOW INDICATED in relapsed or refractory mantle cell lymphoma (MCL)

Dear State Society,

Celgene Corporation is pleased to announce that REVLIMID® (lenalidomide) is now indicated for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.

ICD-9 Diagnostic Code

- The ICD-9 diagnostic code for mantle cell lymphoma is 200.4

Dosage and Administration—MCL

- For relapsed or refractory mantle cell lymphoma, the recommended starting dose of REVLIMID is 25 mg/day orally on Days 1-21 of repeated 28-day cycles. Treatment should be continued until disease progression or unacceptable toxicity
- REVLIMID should be taken orally at about the same time each day, either with or without food
- REVLIMID capsules should be swallowed whole with water
- Inform patients not to break, chew, or open the capsules

Dosage Forms and Strengths

- REVLIMID is available in 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg capsules

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS THROMBOEMBOLISM
See full prescribing information for complete boxed warning.

EMBRYO-FETAL TOXICITY

- **Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death.**
- **Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception.**

REVLIMID is available only through a restricted distribution program called the REVLIMID REMS™ program (formerly known as the "RevAssist® program").

HEMATOLOGIC TOXICITY. REVLIMID can cause significant neutropenia and thrombocytopenia.

- **For patients with del 5q myelodysplastic syndromes, monitor complete blood counts weekly for the first 8 weeks and monthly thereafter.**

VENOUS THROMBOEMBOLISM

- **Significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with multiple myeloma receiving REVLIMID with dexamethasone.**

CONTRAINDICATIONS

Pregnancy:

- REVLIMID can cause fetal harm when administered to a pregnant female. Lenalidomide is contraindicated in females who are pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus

Allergic Reactions:

- REVLIMID is contraindicated in patients who have demonstrated hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide

REVLIMID is only available through a restricted distribution program, REVLIMID REMS™.

Please see accompanying full Prescribing Information, including Boxed WARNINGS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS.

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Important Dosing Information

- The capsules should not be opened, broken, or chewed
- Lenalidomide is primarily excreted unchanged by the kidney. Since elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Monitor renal function
- Monitor CBCs weekly for the first cycle (28 days), every 2 weeks during cycles 2-4, then monthly thereafter
- Treatment is continued or modified based on clinical and laboratory findings
- Dose modification guidelines are recommended to manage Grade 3/4 neutropenia or thrombocytopenia. 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
- For Grade 3 or 4 tumor flare reaction (TFR), recommended to withhold treatment with lenalidomide until TFR resolves to ≤ Grade 1
- Patients may require dose interruption and/or reduction
- Patients may require the use of blood product support and/or growth factors

For relapsed or refractory mantle cell lymphoma, the recommended starting dose of REVLIMID® (lenalidomide) is 25 mg/day orally on Days 1-21 of repeated 28-day cycles. Treatment should be continued until disease progression or unacceptable toxicity.

Treatment is continued, modified, or discontinued based upon clinical and laboratory findings.

Recommended dose adjustments during treatment and restart of treatment

Dose modification guidelines as summarized below are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicities considered to be related to REVLIMID.

Platelet counts

Thrombocytopenia during treatment in MCL

When Platelets	Recommended Course
Fall to <50,000/mcL	Interrupt REVLIMID treatment and follow CBC weekly
Return to ≥50,000/mcL	Resume REVLIMID at 5 mg less than the previous dose. Do not dose below 5 mg daily

Absolute Neutrophil Counts (ANC)

Neutropenia during treatment in MCL

When Neutrophils	Recommended Course
Fall to <1000/mcL for at least 7 days OR Falls to <1,000/mcL with an associated temperature ≥38.5°C OR Falls to <500 /mcL	Interrupt REVLIMID treatment and follow CBC weekly
Return to ≥1,000/mcL	Resume REVLIMID at 5 mg less than the previous dose. Do not dose below 5 mg daily

Other Grade 3/4 Toxicities in MCL

- For other Grade 3/4 toxicities judged to be related to REVLIMID, hold treatment and restart at the physician's discretion at next lower dose level when toxicity has resolved to ≤Grade 2

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Starting Dose Adjustment for Renal Impairment in MCL

Since REVLIMID® (lenalidomide) is primarily excreted unchanged by the kidney, adjustments to the starting dose of REVLIMID are recommended to provide appropriate drug exposure in patients with moderate or severe renal impairment and in patients on dialysis. Based on a pharmacokinetic study in patients with renal impairment due to non-malignant conditions, REVLIMID starting dose adjustment is recommended for patients with CLcr <60 mL/min. Patients not on dialysis with creatinine clearances less than 11 mL/min and dialysis patients with creatinine clearances less than 7 mL/min have not been studied. The recommendations for initial starting doses for patients with MCL are as follows:

Category	Renal Function (Cockcroft-Gault)	Dose in MCL
Moderate Renal Impairment	CLcr 30-60 mL/min	10 mg Every 24 hours
Severe Renal Impairment	CLcr <30 mL/min (not requiring dialysis)	15 mg Every 48 hours
End Stage Renal Disease	CLcr <30 mL/min (requiring dialysis)	5 mg Once daily. On dialysis days, administer the dose following dialysis.

- After initiation of REVLIMID therapy, subsequent REVLIMID dose modification is based on individual patient treatment tolerance

Important Information about REVLIMID REMS™

- To avoid embryo-fetal exposure, REVLIMID is only available through a restricted distribution program called REVLIMID REMS™ (formerly known as the "RevAssist® program")
- REVLIMID can cause fetal harm when administered to a pregnant female. Lenalidomide is contraindicated in females who are pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus
- Effective contraception must be used by female patients of reproductive potential for at least 4 weeks before beginning REVLIMID therapy, during therapy, during dose interruptions and for 4 weeks following discontinuation of REVLIMID therapy
- Females of reproductive potential must have 2 negative pregnancy tests prior to initiating therapy. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing REVLIMID therapy and then weekly during the first month, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles
- If pregnancy does occur during treatment, REVLIMID must be discontinued immediately
- Male Patients: Lenalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID, during dose interruptions and for up to 28 days after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm
- Prescribers and pharmacies certified with REVLIMID REMS™ can prescribe and dispense the product to patients who are enrolled and meet all the conditions of the REVLIMID REMS™ program
- Information about REVLIMID and the REVLIMID REMS™ program can be obtained by calling the Celgene Customer Care Center at 1-888-423-5436, or visiting www.CelgeneRiskManagement.com

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Access Assistance

- Celgene Patient Support® can offer assistance with access to REVLIMID for both insured and uninsured patients. This includes benefits investigations, co-pay assistance, or free drug to those patients who qualify, as well as appeals support
- For assistance or more information, contact your dedicated Celgene Patient Support® Specialist at **1-800-931-8691**, or visit **www.CelgenePatientSupport.com**

For a list of pharmacies certified in the **REVLIMID REMS™** program, visit **www.Celgene.com/PharmacyNetwork**. For more information, or if you have any questions about the new indication for REVLIMID, visit **www.CelgeneRiskManagement.com** or contact your local Celgene representative.

REVLIMID® (lenalidomide) is indicated for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.

Important Safety Information

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS THROMBOEMBOLISM

Embryo-Fetal Toxicity

Do not use REVLIMID during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting REVLIMID treatment. Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after REVLIMID treatment. To avoid embryo-fetal exposure to lenalidomide, REVLIMID is only available through a restricted distribution program, the REVLIMID REMS™ program (formerly known as the "RevAssist®" program).

Information about the REVLIMID REMS™ Program is available at www.celgeneriskmanagement.com or by calling the manufacturer's toll-free number 1-888-423-5436.

Hematologic Toxicity (Neutropenia and Thrombocytopenia)

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

Venous Thromboembolism

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

Important Safety Information continues on next page.

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Important Safety Information (cont'd)

CONTRAINDICATIONS

Pregnancy:

- REVLIMID can cause fetal harm when administered to a pregnant female. Lenalidomide is contraindicated in females who are pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus

Allergic Reactions:

- REVLIMID is contraindicated in patients who have demonstrated hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity:

- REVLIMID is an analogue of thalidomide, a known human teratogen that causes life-threatening human birth defects or embryo-fetal death. An embryo-fetal development study in monkeys indicated that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy, similar to birth defects observed in humans following exposure to thalidomide during pregnancy
- Females of Reproductive Potential: Must avoid pregnancy for at least 4 weeks before beginning REVLIMID therapy, during therapy, during dose interruptions and for at least 4 weeks after completing therapy. Must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control beginning 4 weeks prior to initiating treatment with REVLIMID, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of REVLIMID therapy. Must obtain 2 negative pregnancy tests prior to initiating therapy
- Males: Lenalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 28 days after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm
- Blood Donation: Patients must not donate blood during treatment with REVLIMID and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to REVLIMID

REVLIMID REMS Program

Because of embryo-fetal risk, REVLIMID is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) the **REVLIMID REMS** Program **(formerly known as the "RevAssist®" Program)**. Prescribers and pharmacies must be certified with the program and patients must sign an agreement form and comply with the requirements. Further information about the **REVLIMID REMS** program is available at www.celgeneriskmanagement.com or by telephone at 1-888-423-5436.

Hematologic Toxicity: REVLIMID can cause significant neutropenia and thrombocytopenia. Patients may require dose interruption and/or dose reduction. **MCL:** Patients taking REVLIMID for MCL should have their complete blood counts monitored weekly for the first cycle (28 days), every 2 weeks during cycles 2-4, and then monthly thereafter. In the MCL trial, Grade 3 or 4 neutropenia was reported in 43% of the patients. Grade 3 or 4 thrombocytopenia was reported in 28% of the patients.

Venous Thromboembolism: Venous thromboembolic events (predominantly deep venous thrombosis and pulmonary embolism) have occurred in patients with MCL treated with lenalidomide monotherapy. It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with REVLIMID may lessen the potential for venous thromboembolism. The decision to take prophylactic measures should be done carefully after assessment of the individual patient's underlying risk factors.

Important Safety Information continues on next page.

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Important Safety Information (cont'd)

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

Tumor Lysis Syndrome: Fatal instances of tumor lysis syndrome (TLS) have been reported during treatment with lenalidomide. The patients at risk of TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Tumor Flare Reaction: Tumor flare reaction (TFR) occurred during investigational use of lenalidomide for chronic lymphocytic leukemia (CLL) and lymphoma, and is characterized by tender lymph node swelling, low grade fever, pain and rash. Treatment of CLL with lenalidomide outside of a well-monitored clinical trial is discouraged.

Monitoring and evaluation for TFR is recommended in patients with MCL. Tumor flare may mimic the progression of disease (PD). In patients with Grade 3 or 4 TFR, it is recommended to withhold treatment with lenalidomide until TFR resolves to ≤Grade 1. In the MCL trial, approximately 10% of subjects experienced TFR; all reports were Grade 1 or 2 in severity. All of the events occurred in cycle 1 and one patient developed TFR again in cycle 11. Lenalidomide may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician's discretion. Patients with Grade 1 or 2 TFR may also be treated with corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and/or narcotic analgesics for management of TFR symptoms. Patients with Grade 3 or 4 TFR may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR.

Hepatotoxicity: Hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dexamethasone. The mechanism of drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop Revlimid upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

Second Primary Malignancies: Patients with MM treated with lenalidomide in studies including melphalan and stem cell transplantation had a higher incidence of second primary malignancies, particularly acute myelogenous leukemia (AML) and Hodgkin lymphoma, compared to patients in the control arms who received similar therapy but did not receive lenalidomide. Monitor patients for the development of second malignancies. Take into account both the potential benefit of lenalidomide and the risk of second primary malignancies when considering treatment with lenalidomide.

ADVERSE REACTIONS

Mantle Cell Lymphoma

- Grade 3 and 4 adverse events reported in ≥5% of patients treated with REVLIMID in the MCL trial (N=134) included neutropenia (43%), thrombocytopenia (28%), anemia (11%), pneumonia (9%), leukopenia (7%), fatigue (7%), diarrhea (6%), dyspnea (6%), and febrile neutropenia (6%)
- Serious adverse events reported in ≥2 patients treated with REVLIMID monotherapy for MCL included chronic obstructive pulmonary disease, clostridium difficile colitis, sepsis, basal cell carcinoma, and supraventricular tachycardia
- Adverse events reported in ≥15% of patients treated with REVLIMID in the MCL trial included neutropenia (49%), thrombocytopenia (36%), fatigue (34%), anemia (31%), diarrhea (31%), nausea (30%), cough (28%), pyrexia (23%), rash (22%), dyspnea (18%), pruritus (17%), peripheral edema (16%), constipation (16%), and leukopenia (15%)
- Adverse events occurring in patients treated with REVLIMID in the MCL trial resulted in at least one dose interruption in 76 (57%) patients, at least one dose reduction in 51 (38%) patients, and discontinuation of treatment in 26 (19%) patients

Important Safety Information continues on next page.

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Important Safety Information (cont'd)

DRUG INTERACTIONS

Periodic monitoring of digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, is recommended during administration of REVLIMID.

USE IN SPECIFIC POPULATIONS

Pregnancy: If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure to REVLIMID must be reported to the FDA via the MedWatch program at 1-800-332-1088 and also to Celgene Corporation at 1-888-423-5436.

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

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

Geriatric Use: Since elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Monitor renal function

Renal Impairment: Since REVLIMID is primarily excreted unchanged by the kidney, adjustments to the starting dose of REVLIMID are recommended to provide appropriate drug exposure in patients with moderate (CLcr 30-60 mL/min) or severe renal impairment (CLcr <30 mL/min) and in patients on dialysis.

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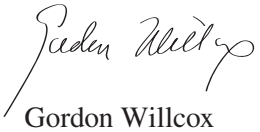
Sincerely,



Gordon Willcox

Executive Director, Market Access
Celgene Corporation

To report SUSPECTED ADVERSE REACTIONS or embryo-fetal exposure, contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-332-1088 or www.fda.gov/medwatch.

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