What is REVLIMID?
REVLIMID® (lenalidomide) capsule is an oral thalidomide analogue therapy 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.

REVLIMID was approved for this indication by the U.S. Food and Drug Administration (FDA) on June 5.

What is MCL?
MCL is a subtype of B-cell non-Hodgkin’s lymphoma (NHL), a blood cancer in which lymphocytes accumulate in one or more lymph nodes, causing tumors known as lymphomas. Less than ten percent of NHL patients have this fast-growing form, which is likely to spread to the lymph nodes, spleen, bone marrow, blood, and gastrointestinal system. MCL has the poorest long-term survival of all B-cell lymphoma subtypes, with fewer than 50 percent of patients surviving at 5 years.

Treatment for MCL is poorly defined, in part due to the relative rarity of this subtype of NHL, and there remains no standard of care for patients with relapsed/refractory MCL.
How does REVLIMID work?
REVLIMID belongs to Celgene’s class of cancer drugs called IMiDs compounds, which are small molecule, orally available therapies that modulate the immune system and other biological targets through multiple mechanisms of action, not all of which have been fully characterized.

REVLIMID Acts in the Microenvironment of the Cancer Cell
REVLIMID is thought to work by:
• INHIBITING MCL cell growth and proliferations
• INTERFERING with expression of genes in MCL cells
• KILLING MCL cells directly, by destroying the cells’ internal structural support system
• RESTORING immune-mediated antitumor action

What has the clinical data for REVLIMID shown for patients with MCL?
This approval was based on the results of MCL-001, a phase II, multi-center, single arm, open-label study evaluating REVLIMID (25 mg once per day on days 1-21 of each 28-day cycle) in 134 patients with MCL who had received prior treatment with rituximab, cyclophosphamide, an anthracycline (or mitoxantrone), and bortezomib alone or in combination.

In the study, overall response rate (the primary endpoint of the trial) was 26% (34/133) with a complete response rate of 7% (9/133). The median duration of response was 16.6 months (95% CI, 7.7-26.7).

The most common grade 3/4 adverse events reported in ≥5% of patients were neutropenia (43%), thrombocytopenia (28%), anemia (11%), pneumonia (9%), fatigue (7%), leukopenia (7%), febrile neutropenia (7%), diarrhea (6%) and dyspnea (6%).

U.S. Regulatory Information for REVLIMID
REVLIMID® (lenalidomide) is indicated for the treatment of patients with relapsed or refractory mantle cell lymphoma (MCL) after prior therapy that 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.
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.

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

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 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.

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