Mylomid

Lenalidomide INN 10 mg & 25 mg Capsule

COMPOSITION
Mylomid-10: Each Capsule contains Lenalidomide INN 10 mg.
Mylomid-25: Each capsule contains Lenalidomide INN 25 mg.

CLINICAL PHARMACOLOGY
Mechanism of Action:
Lenalidomide is an analogue of thalidomide with immunomodulatory, antiangiogenic, and antineoplastic properties. Cellular activities of Lenalidomide are mediated through its target cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex. In vitro, in the presence of drug, substrate proteins (including Aiolos, Ikaros, and CK1α) are targeted for ubiquitination and subsequent degradation leading to direct cytotoxic and immunomodulatory effects. Lenalidomide inhibits proliferation and induces apoptosis of certain hematopoietic tumor cells including MM, mantle cell lymphoma, and del (5q) myelodysplastic syndromes in vitro. Lenalidomide causes a delay in tumor growth in some in vivo nonclinical hematopoietic tumor models including MM. Immunomodulatory properties of Lenalidomide include increased number and activation of T cells and natural killer (NK) cells leading to direct and enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) via increased secretion of interleukin-2 and interferon-gamma, increased numbers of NKT cells, and inhibition of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. In MM cells, the combination of Lenalidomide and Dxamethasone synergizes the inhibition of cell proliferation and the induction of apoptosis.
Pharmacokinetics:
Absorption: Lenalidomide is rapidly absorbed following oral administration. Following single and multiple doses of Lenalidomide in patients with MM or MDS, the maximum plasma concentrations occurred between 0.5 and 6 hours post-dose. The single and multiple dose pharmacokinetic disposition of Lenalidomide is linear with AUC and Cmax values increasing proportionally with dose. Multiple doses of Lenalidomide at the recommended dosage does not result in drug accumulation. Administration of a single 25 mg dose of Lenalidomide with a high-fat meal in healthy subjects reduces the extent of absorption, with an approximate 20% decrease in AUC and 50% decrease in Cmax. In the trials where the efficacy and safety were established for Lenalidomide, the drug was administered without regard to food intake. Lenalidomide can be administered with or without food. The oral absorption rate of Lenalidomide in patients with MCL is similar to that observed in patients with MM or MDS.
Distribution: In vitro [^{14}C]-Lenalidomide binding to plasma proteins is approximately 30%. Lenalidomide is present in semen at 2 hours (1379 ng;ejaculate) and 24 hours (35 ng;ejaculate) after the administration of Lenalidomide 25 mg daily.
Elimination: The mean half-life of Lenalidomide is 3 hours in healthy subjects and 3 to 5 hours in patients with MM, MDS or MCL.
Metabolism: Lenalidomide undergoes limited metabolism. Unchanged Lenalidomide is the predominant circulating component in humans. Two identified metabolites are 5¬ Hydroxy-Lenalidomide and N-Acetyl-Lenalidomide; each constitutes less than 5% of parent levels in circulation.
Excretion: Elimination is primarily renal. Following a single oral administration of [^{14}C]-Lenalidomide 25 mg to healthy subjects, approximately 90% and 4% of the radioactive dose was eliminated within ten days in urine and feces, respectively. Approximately 82% of the radioactive dose was excreted as Lenalidomide in the urine within 24 hours. Hydroxy-Lenalidomide and N-Acetyl-Lenalidomide represented 4.6% and 1.8% of the excreted dose, respectively. The renal clearance of Lenalidomide exceeds the glomerular filtration rate.

INDICATIONS
Multiple Myeloma: Lenalidomide in combination with Dexamethasone is indicated for the treatment of adult patients with multiple myeloma (MM). Lenalidomide is indicated as maintenance therapy in adult patients with MM following autologous hematopoietic stem cell transplantation (auto-HSCT).
Myelodysplastic Syndromes: Lenalidomide is indicated for the treatment of adult patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.
Mantle Cell Lymphoma: Lenalidomide is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included Bortezomib.
Follicular Lymphoma: Lenalidomide in combination with a Rituximab product, is indicated for the treatment of adult patients with previously treated follicular lymphoma (FL).
Marginal Zone Lymphoma: Lenalidomide in combination with a Rituximab product, is indicated for the treatment of adult patients with previously treated marginal zone lymphoma (MZL).
Limitations of Use: Lenalidomide is not indicated and is not recommended for the treatment of patients with CLL outside of controlled clinical trials.

DOSAGE AND ADMINISTRATION
Recommended Dosage for Multiple Myeloma:
Lenalidomide Combination Therapy:
The recommended starting dose of Lenalidomide is 25 mg orally once daily on Days 1-21 of repeated 28-day cycles in combination with Dexamethasone. For patients greater than 75 years old, the starting dose of Dexamethasone may be reduced. Treatment should be continued until disease progression or unacceptable toxicity.
In patients who are not eligible for auto-HSCT, treatment should continue until disease progression or unacceptable toxicity. For patients who are auto-HSCT-eligible, hematopoietic stem cell mobilization should occur within 4 cycles of a Lenalidomide -containing therapy.
Dose Adjustments for Hematologic Toxicities During MM Treatment :
Dose modification guidelines, as summarized in Table 1 below, are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicity judged to be related to Lenalidomide.

Table 1: Dose Adjustments for Hematologic Toxicities for MM

Platelet counts	
Thrombocytopenia in MM	
When Platelets	**Recommended Course Days 1-21 of repeated 28-day cycle**
Fall below 30,000/mcL	Interrupt Lenalidomide treatment, follow CBC weekly
Return to at least 30,000/mcL	Resume Lenalidomide at next lower dose. Do not dose below 2.5 mg daily
For each subsequent drop below 30,000/mcL Return to at least 30,000/mcL	Interrupt Lenalidomide treatment Resume Lenalidomide at next lower dose. Do not dose below 2.5 mg daily
Absolute Neutrophil counts (ANC)	
Neutropenia in MM	
When Neutrophils	**Recommended Course Days 1-21 of repeated 28-day cycle**
Fall below 1000/mcL Return to at least 1,000/mcL and neutropenia is the only toxicity	Interrupt Lenalidomide treatment, follow CBC weekly Resume Lenalidomide at 25 mg daily or initial starting dose
Return to at least 1,000/mcL and if other toxicity	Resume Lenalidomide at next lower dose. Do not dose below 2.5 mg daily
For each subsequent drop below 1,000/mcL Return to at least 1,000/mcL	Interrupt Lenalidomide treatment Resume Lenalidomide at next lower dose. Do not dose below 2.5 mg daily

Lenalidomide Maintenance Therapy Following Auto-HSCT:
Following auto-HSCT, initiate Lenalidomide maintenance therapy after adequate hematologic recovery (ANC at least 1000;mcL and;or platelet counts at least 75,000;mcL). The recommended starting dose of Lenalidomide is 10 mg once daily continuously (Days 1-28 of repeated 28-day cycles) until disease progression or unacceptable toxicity. After 3 cycles of maintenance therapy, the dose can be increased to 15 mg once daily if tolerated.
Dose Adjustments for Hematologic Toxicities During MM Treatment:
Dose modification guidelines, as summarized in Table 2 below, are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicity judged to be related to Lenalidomide.

Table 2: Dose Adjustments for Hematologic Toxicities for MM

Platelet counts	
Thrombocytopenia in MM	
When Platelets	**Recommended Course**
Fall below 30,000/mcL	Interrupt Lenalidomide treatment, follow CBC weekly
Return to at least 30,000/mcL	Resume Lenalidomide at next lower dose, continuously for Days 1-28 of repeated 28-day cycle
If at the 5 mg daily dose, For a subsequent drop below 30,000/mcL	Interrupt Lenalidomide treatment. Do not dose below 5mg daily for Day 1 to 21 of 28 day cycle
Return to at least 30,000/mcL	Resume Lenalidomide at 5 mg daily for Days 1 to 21of 28-day cycle. Do not dose below 5 mg daily for Day 1 to 21 of 28 day cycle
Absolute Neutrophil counts (ANC)	
Neutropenia in MM	
When Neutrophils	**Recommended Course**
Fall below 500/mcL Return to at least 500/mcL	Interrupt Lenalidomide treatment, follow CBC weekly Resume Lenalidomide at next lower dose, continuously for Days 1-28 of repeated 28-day cycle
If at 5 mg daily dose, For a subsequent drop below 500/mcL	Interrupt Lenalidomide treatment. Do not dose below 5mg daily for Days 1 to 21 of 28-day cycle
Return to at least 500/mcL	Resume Lenalidomide at 5 mg daily for Days 1 to 21 of 28-day cycle. Do not dose below 5 mg daily for Days 1 to 21 of 28-day cycle

Other Toxicities in MM:
For other Grade 3;4 toxicities judged to be related to Lenalidomide, hold treatment and restart at the physician's discretion at next lower dose level when toxicity has resolved to Grade 2 or lower.
Recommended Dosage for Myelodysplastic Syndromes:
The recommended starting dose of Lenalidomide is 10 mg daily. Treatment is continued or modified based upon clinical and laboratory findings. Continue treatment until disease progression or unacceptable toxicity.
Dose Adjustments for Hematologic Toxicities During MDS Treatment:
Patients who are dosed initially at 10 mg and who experience thrombocytopenia should have their dosage adjusted as follows:
Platelet counts
If thrombocytopenia develops WITHIN 4 weeks of starting treatment at 10 mg daily in MDS:

If baseline is at least 100,000/mcL	
When Platelets	**Recommended Course**
Fall below 50,000/mcL Return to at least 50,000/mcL	Interrupt Lenalidomide treatment Resume Lenalidomide at 5 mg daily
If baseline is below 100,000/mcL	
When Platelets	**Recommended Course**
Fall to 50% of the baseline value	Interrupt Lenalidomide treatment
If baseline is at least 60,000/mcL and returns to at least 50,000/mcL	Resume Lenalidomide at 5 mg daily
If baseline is below 60,000/mcL and returns to at least 30,000/mcL	Resume Lenalidomide at 5 mg daily

If thrombocytopenia develops AFTER 4 weeks of starting treatment at 10 mg daily in MDS:

When Platelets	**Recommended Course**
Fall below 30,000/mcL or below 50,000/mcL with platelet transfusions	Interrupt Lenalidomide treatment
Return to at least 30,000/mcL (without hemostatic failure)	Resume Lenalidomide at 5 mg daily

Patients who experience thrombocytopenia at 5 mg daily should have their dosage adjusted as follows:
If thrombocytopenia develops during treatment at 5 mg daily in MDS:

When Platelets	**Recommended Course**
Fall below 30,000/mcL or below 50,000/mcL with platelet transfusions	Interrupt Lenalidomide treatment
Return to at least 30,000/mcL (without hemostatic failure)	Resume Lenalidomide at 2.5 mg daily

Patients who are dosed initially at 10 mg and experience neutropenia should have their dosage adjusted as follows:
Absolute Neutrophil counts (ANC)
If neutropenia develops WITHIN 4 weeks of starting treatment at 10 mg daily in MDS:

If baseline ANC is at least 1,000/mcL	
When Neutrophils	**Recommended Course**
Fall below 750/mcL	Interrupt Lenalidomide treatment
Return to at least 1,000/mcL	Resume Lenalidomide at 5 mg daily
If baseline ANC is below 1,000/mcL	
When Neutrophils	**Recommended Course**
Fall below 500/mcL	Interrupt Lenalidomide treatment
Return to at least 500/mcL	Resume Lenalidomide at 5 mg daily

If neutropenia develops AFTER 4 weeks of starting treatment at 10 mg daily in MDS:

When Neutrophils	**Recommended Course**
Fall below 500/mcL for at least 7 days or below 500/mcL associated with fever (at least 38.5°C)	Interrupt Lenalidomide treatment
Return to at least 500/mcL	Resume Lenalidomide at 5 mg daily

Patients who experience neutropenia at 5 mg daily should have their dosage adjusted as follows:
If neutropenia develops during treatment at 5 mg daily in MDS:

When Neutrophils	**Recommended Course**
Fall below 500/mcL for at least 7 days or below 500/mcL associated with fever (at least 38.5°C)	Interrupt Lenalidomide treatment
Return to at least 500/mcL	Resume Lenalidomide at 2.5 mg daily

Other Grade 3 / 4 Toxicities in MDS:
For other Grade 3;4 toxicities judged to be related to Lenalidomide, hold treatment and restart at the physician's discretion at next lower dose level when toxicity has resolved to Grade 2 or lower.
Recommended Dosage for Mantle Cell Lymphoma:
The recommended starting dose of Lenalidomide is 25 mg;day orally on Days 1-21 of repeated 28-day cycles for relapsed or refractory mantle cell lymphoma. Treatment should be continued until disease progression or unacceptable toxicity.
Treatment is continued, modified or discontinued based upon clinical and laboratory findings.
Dose Adjustments for Hematologic Toxicities During MCL 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 Lenalidomide.

Platelet counts	
Thrombocytopenia during treatment in MCL	
When Platelets	**Recommended Course**
Fall below 50,000/mcL	Interrupt Lenalidomide treatment, follow CBC weekly
Return to at least 50,000/mcL	Resume Lenalidomide 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 below 1000/mcL for at least 7 days OR Falls below 1,000/mcL with an associated temperature at least 38.5°C OR Falls below 500/mcL	Interrupt Lenalidomide treatment and follow CBC weekly
Return to at least 1,000/mcL	Resume Lenalidomide 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 Lenalidomide, hold treatment and restart at the physician's discretion at next lower dose level when toxicity has resolved to Grade 2 or lower.

Recommended Dosage for Follicular Lymphoma or Marginal Zone Lymphoma:
The recommended starting dose of Lenalidomide is 20 mg orally once daily on Days 1-21 of repeated 28-day cycles for up to 12 cycles of treatment in combination with a Rituximab-product. For dose adjustments due to toxicity with Rituximab, refer to the product prescribing information.
Dose Adjustments for Hematologic Toxicities during FL or MZL Treatment:
Dose modification guidelines, as summarized below, are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicity judged to be related to Lenalidomide.

Platelet counts	
Thrombocytopenia during treatment in FL or MZL	
When Platelets	**Recommended Course**
Fall below 50,000/mcL	Interrupt Lenalidomide treatment, follow CBC weekly
Return to at least 50,000/mcL	If patient starting dose was 20 mg daily, resume Lenalidomide at 5 mg less than the previous dose. Do not dose below 5 mg daily. If patient starting dose was 10 mg daily, resume at 5 mg less than previous dose. Do not dose below 2.5 mg daily.
Absolute Neutrophil counts (ANC)	
Neutropenia during treatment in FL or MZL	
When Neutrophils	**Recommended Course**
Fall below 1000/mcL for at least 7 days OR Falls below 1,000/mcL with an associated temperature at least 38.5°C OR Falls below 500/mcL	Interrupt Lenalidomide treatment and follow CBC weekly
Return to at least 1,000/mcL	If patient starting dose was 20 mg daily, resume Lenalidomide at 5 mg less than the previous dose. Do not dose below 5 mg daily. If patient starting dose was 10 mg daily, resume at 5 mg less than previous dose. Do not dose below 2.5 mg daily.

Other Grade 3 / 4 Toxicities FL or MZL:
For other Grade 3/4 toxicities judged to be related to Lenalidomide, hold treatment and restart at the physician's discretion at next lower dose level when toxicity has resolved to Grade 2 or below.

Recommended Dosage for Patients with Renal Impairment:
The recommendations for dosing patients with renal impairment are shown in the following table.

Table 3: Dose Adjustments for Patients with Renal Impairment

Renal Function (Cockcroft-Gault)	**Dose in Lenalidomide Combination Therapy for MM and MCL**	**Dose in Lenalidomide Combination Therapy for FL and MZL**	**Dose in Lenalidomide Maintenance Therapy Following Auto-HSCT for MM and for MDS**
CLcr 30 to 60 mL/min	10 mg once daily	10 mg once daily	5 mg once daily
CLcr below 30 mL/min (not requiring dialysis)	15 mg every other day	5 mg once daily	2.5 mg once daily
CLcr below 30 mL/min (requiring dialysis)	5 mg once daily. On dialysis days, administer the dose following dialysis.	5 mg once daily. On dialysis days, administer the dose following dialysis.	2.5 mg once daily. On dialysis days, administer the dose following dialysis.

Lenalidomide Combination Therapy for MM: For CLcr of 30 to 60 mL/min, consider escalating the dose to 15 mg after 2 cycles if the patient tolerates the 10 mg dose of Lenalidomide without dose-limiting toxicity.
Lenalidomide Maintenance Therapy Following Auto-HSCT for MM and for MCL and MDS: Base subsequent Lenalidomide dose increase or decrease on individual patient treatment tolerance.
Lenalidomide Combination Therapy for FL or for MZL: For patients with CLcr of 30 to 60 mL/min, after 2 cycles, the Lenalidomide dose may be increased to 15 mg orally if the patient has tolerated therapy. Or, as directed by the registered physicians.
ADMINISTRATION Patients should be advised to take Lenalidomide orally at about the same time each day, either with or without food. Patients should be advised to swallow Lenalidomide capsules whole with water and not to open, break, or chew them.

DRUG INTERACTIONS
Digoxin: When Digoxin was co-administered with multiple doses of Lenalidomide (10 mg/day) the Digoxin Cmax and AUCinf were increased by 14%. 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 Lenalidomide.
Concomitant Therapies That May Increase the Risk of Thrombosis: Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution after making a benefit-risk assessment in patients receiving Lenalidomide.
Warfarin: Co-administration of multiple doses of Lenalidomide (10 mg/day) with a single dose of Warfarin (25 mg) had no effect on the pharmacokinetics of Lenalidomide or R- and S-Warfarin. Expected changes in laboratory assessments of PT and INR were observed after Warfarin administration, but these changes were not affected by concomitant Lenalidomide administration. It is not known whether there is an interaction between Dexamethasone and Warfarin. Close monitoring of PT and INR is recommended in patients with MM taking concomitant Warfarin.

CONTRAINDICATIONS
Pregnancy: Lenalidomide can cause fetal harm when administered to a pregnant female. Limb abnormalities were seen in the offspring of monkeys that were dosed with Lenalidomide during organogenesis. This effect was seen at all doses tested. Due to the results of this developmental monkey study, and Lenalidomide's structural similarities to Thalidomide, a known human teratogen, 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 risk to a fetus.
Allergic Reactions: Lenalidomide is contraindicated in patients who have demonstrated hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to Lenalidomide.

PRECAUTIONS
Lenalidomide REMS Program: Because of the embryo-fetal risk, Lenalidomide is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS), the Lenalidomide REMS program.
Required components of the Lenalidomide REMS program include the following: • Prescribers must be certified with the Lenalidomide REMS program by enrolling and complying with the REMS requirements. • Patients must sign a Patient-Physician agreement form and comply with the REMS requirements. In particular, female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements and males must comply with contraception requirements. • Pharmacies must be certified with the Lenalidomide REMS program, must only dispense to patients who are authorized to receive Lenalidomide and comply with REMS requirements.
Hematologic Toxicity:
Lenalidomide can cause significant neutropenia and thrombocytopenia. Monitor patients with neutropenia for signs of infection. Advise patients to observe for bleeding or bruising, especially with use of concomitant medication that may increase risk of bleeding. Patients taking Lenalidomide should have their complete blood counts assessed periodically as described below.
Monitor complete blood counts (CBC) in patients taking Lenalidomide in combination with Dexamethasone or as Lenalidomide maintenance therapy for MM every 7 days (weekly) for the first 2 cycles, on Days 1 and 15 of Cycle 3, and every 28 days (4 weeks) thereafter. A dose interruption and/or dose reduction may be required .In the MM maintenance therapy trials, Grade 3 or 4 neutropenia was reported in up to 59% of Lenalidomide -treated patients and Grade 3 or 4 thrombocytopenia in up to 38% of Lenalidomide -treated patients.
Monitor complete blood counts (CBC) in patients taking Lenalidomide for MDS weekly for the first 8 weeks and at least monthly thereafter. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the MDS study. In the 48% of patients who developed Grade 3 or 4 neutropenia, the median time to onset was 42 days (range, 14-411 days), and the median time to documented recovery was 17 days (range, 2-170 days). In the 54% of patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was 28 days (range, 8-290 days), and the median time to documented recovery was 22 days (range, 5-224 days).
Monitor complete blood counts (CBC) in patients taking Lenalidomide for MCL weekly for the first cycle (28 days), every 2 weeks during cycles 2-4, and then monthly thereafter. Patients may require dose interruption and/or dose reduction. 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.
Monitor complete blood counts (CBC) in patients taking Lenalidomide for FL or MZL weekly for the first 3 weeks of Cycle 1 (28 days), every 2 weeks during Cycles 2-4, and then monthly thereafter. Patients may require dose interruption and/or dose reduction. In the AUGMENT and MAGNIFY trials, Grade 3 or 4 neutropenia was reported in 50% and 33%, respectively, of patients in the Lenalidomide +Rituximab arm. Grade 3 or 4 thrombocytopenia was reported in 2% and 8%, respectively, of patients in the Lenalidomide +Rituximab arm.
Venous and Arterial Thromboembolism:
Venous thromboembolic events (VTE [DVT and PE]) and arterial thromboembolic events (ATE, myocardial infarction and stroke) are increased in patients treated with Lenalidomide.
A significantly increased risk of DVT (7.4%) and of PE (3.7%) occurred in patients with MM after at least one prior therapy who were treated with Lenalidomide and Dexamethasone therapy compared to patients treated in the placebo and Dexamethasone group (3.1% and 0.9%) in clinical trials with varying use of anticoagulant therapies. In the newly diagnosed multiple myeloma (NDMM) study in which nearly all patients received antithrombotic prophylaxis, DVT was reported as a serious adverse reaction (3.6%, 2.0%, and 1.7%) in the Rd Continuous, Rd18, and MPT Arms, respectively. The frequency of serious adverse reactions of PE was similar between the Rd Continuous, Rd18, and MPT Arms (3.8%, 2.8%, and 3.7%, respectively).
Myocardial infarction (1.7%) and stroke (CVA) (2.3%) are increased in patients with MM after at least one prior therapy who were treated with Lenalidomide and Dexamethasone therapy compared to patients treated with placebo and Dexamethasone (0.6%, and 0.9%) in clinical trials. In the NDMM study, myocardial infarction (including acute) was reported as a serious adverse reaction (2.3%, 0.6%, and 1.1%) in the Rd Continuous, Rd18, and MPT Arms, respectively. The frequency of serious adverse reactions of CVA was similar between the Rd Continuous, Rd18, and MPT Arms (0.8%, 0.6 %, and 0.6%, respectively).
Patients with known risk factors, including prior thrombosis, may be at greater risk and actions should be taken to try to minimize all modifiable factors (e.g. hyperlipidemia, hypertension, smoking).
In controlled clinical trials that did not use concomitant thromboprophylaxis, 21.5% overall thrombotic events (Standardized MedDRA Query Embolic and Thrombotic events) occurred in patients with refractory and relapsed MM who were treated with Lenalidomide and Dexamethasone compared to 8.3% thrombosis in patients treated with placebo and Dexamethasone. The median time to first thrombosis event was 2.8 months. In the NDMM study in which nearly all patients received antithrombotic prophylaxis, the overall frequency of thrombotic events was 17.4% in patients in the combined Rd Continuous and Rd18 Arms, and was 11.6% in the MPT Arm. The median time to first thrombosis event was 4.3 months in the combined Rd Continuous and Rd18 Arms.
In the AUGMENT trial, the incidence of VTE (including DVT and PE) in FL or MZL patients was 3.4% in the Lenalidomide +Rituximab arm. In the AUGMENT trial, the incidence of ATE (including MI) in FL or MZL patients was 0.6% in the Lenalidomide +Rituximab arm.
Thromboprophylaxis is recommended. The regimen of thromboprophylaxis should be based on an assessment of the patient's underlying risks. Instruct patients to report immediately any signs and symptoms suggestive of thrombotic events. ESAs and estrogens may further increase the risk of thrombosis and their use should be based on a benefit-risk decision in patients receiving Lenalidomide.
Increased Mortality in Patients with CLL: In a prospective randomized (1:1) clinical trial in the first line treatment of patients with chronic lymphocytic leukemia, single agent Lenalidomide therapy increased the risk of death as compared to single agent Chlorambucil. In an interim analysis, there were 34 deaths among 210 patients on the Lenalidomide treatment arm compared to 18 deaths among 211 patients in the Chlorambucil treatment arm, and hazard ratio for overall survival was 1.92 [95% CI: 1.08 – 3.41], consistent with a 92% increase in the risk of death. The trial was halted for safety in July 2013. Serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure occurred more frequently in the Lenalidomide treatment arm. Lenalidomide is not indicated and not recommended for use in CLL outside of controlled clinical trials.
Second Primary Malignancies:
In clinical trials in patients with MM receiving Lenalidomide, an increase of hematologic plus solid tumor second primary malignancies (SPM) notably AML and MDS have been observed. An increase in hematologic SPM including AML and MDS occurred in 5.3% of patients with NDMM receiving Lenalidomide in combination with oral melphalan compared with 1.3% of patients receiving melphalan without Lenalidomide. The frequency of AML and MDS cases in patients with NDMM treated with Lenalidomide in combination with dexamethasone without melphalan was 0.4%.
In patients receiving Lenalidomide maintenance therapy following high dose intravenous melphalan and auto-HSCT, hematologic SPM occurred in 7.5% of patients compared to 3.3% in patients receiving placebo. The incidence of hematologic plus solid tumor (excluding squamous cell carcinoma and basal cell carcinoma) SPM was 14.9%, compared to 8.8% in patients receiving placebo with a median follow-up of 91.5 months. Non-melanoma skin cancer SPM, including squamous cell carcinoma and basal cell carcinoma, occurred in 3.9% of patients receiving Lenalidomide maintenance, compared to 2.6% in the placebo arm.
In patients with relapsed or refractory MM treated with Lenalidomide +Dexamethasone, the incidence of hematologic plus solid tumor (excluding squamous cell carcinoma and basal cell carcinoma) SPM was 2.3% versus 0.6% in the Dexamethasone alone arm. Non-melanoma skin cancer SPM, including squamous cell carcinoma and basal cell carcinoma, occurred in 3.1% of patients receiving Lenalidomide +Dexamethasone, compared to 0.6% in the Dexamethasone alone arm.
Patients who received Lenalidomide -containing therapy until disease progression did not show a higher incidence of invasive SPM than patients treated in the fixed duration Lenalidomide -containing arms. Monitor patients for the development of second primary malignancies. Take into account both the potential benefit of Lenalidomide and the risk of second primary malignancies when considering treatment with Lenalidomide.
In the AUGMENT trial with FL or MZL patients receiving Lenalidomide +Rituximab therapy, hematologic plus solid tumor SPMs, notably AML, have been observed. In the AUGMENT trial, hematologic SPM of AML occurred in 0.6% of patients with FL or MZL receiving Lenalidomide +Rituximab therapy. The incidence of hematologic plus solid tumor SPMs (excluding nonmelanoma skin cancers) was 1.7% in the Lenalidomide +Rituximab arm with a median follow-up of 29.8 months (range 0.5 to 51.3 months). Monitor patients for the development of second primary malignancies. Take into account both the potential benefit of Lenalidomide and the risk of second primary malignancies when considering treatment with Lenalidomide.
Increased Mortality in Patients with MM When Pembrolizumab Is Added to a Thalidomide Analogue and Dexamethasone:
In two randomized clinical trials in patients with MM, the addition of Pembrolizumab to a Thalidomide analogue plus Dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with MM with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus Dexamethasone is not recommended outside of controlled clinical trials.
Hepatotoxicity: Hepatic failure, including fatal cases, has occurred in patients treated with Lenalidomide in combination with Dexamethasone. In clinical trials, 15% of patients experienced hepatotoxicity (with hepatocellular, cholestatic and mixed characteristics); 2% of patients with MM and 1% of patients with myelodysplasia had serious hepatotoxicity events. 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 Lenalidomide upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.
Severe Cutaneous Reactions Including Hypersensitivity Reactions:
Angioedema and severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive Lenalidomide. Lenalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Lenalidomide must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS, TEN or DRESS is suspected and should not be resumed following discontinuation for these reactions.
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. Monitor patients at risk closely and take appropriate preventive approaches. In the AUGMENT trial in FL or MZL patients, TLS occurred in 2 patients (1.1%) in the Lenalidomide +Rituximab arm. TLS occurred in 1 patient (0.5%) in the MAGNIFY trial during the Lenalidomide +Rituximab induction period; the event was a serious, Grade 3 adverse reaction.
Tumor Flare Reaction: Tumor are reaction (TFR) has occurred during investigational use of Lenalidomide for CLL and lymphoma, and is characterized by tender lymph node swelling, low grade fever, pain and rash. Lenalidomide is not indicated and not recommended for use in CLL outside of controlled clinical trials.
Monitoring and evaluation for TFR is recommended in patients with MCL, FL, or MZL. Tumor are reaction may mimic progression of disease (PD).
In the MCL trial, 13/134 (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. In the AUGMENT trial in FL or MZL patients, TFR was reported in 19/176 (10.8%) of patients in Lenalidomide with Rituximab arm; one patient in the Lenalidomide +Rituximabarm experienced a Grade 3 TFR. In the MAGNIFY trial, 9/222 (4.1%) of patients experienced TFR; all reports were Grade 1 or 2 in severity and 1 event was considered as serious.
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 and 2 TFR may also be treated with corticosteroids, non-steroidal anti-in ammatory drugs (NSAIDs) and/or narcotic analgesics for management of TFR symptoms. In patients with Grade 3 or 4 TFR, it is recommended to withhold treatment with Lenalidomide until TFR resolves to ≤ Grade 1. 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.
Impaired Stem Cell Mobilization: A decrease in the number of CD34+ cells collected after treatment (> 4 cycles) with Lenalidomide has been reported. In patients who are auto-HSCT candidates, referral to a transplant center should occur early in treatment to optimize the timing of the stem cell collection. In patients who received more than 4 cycles of a Lenalidomide -containing treatment or for whom inadequate numbers of CD 34+ cells have been collected with G-CSF alone, G-CSF with cyclophosphamide or the combination of GCSF with a CXCR4 inhibitor may be considered.
Thyroid Disorders: Both hypothyroidism and hyperthyroidism have been reported. Measure thyroid function before start of Lenalidomide treatment and during therapy.
Early Mortality in Patients with MCL: In another MCL study, there was an increase in early deaths (within 20 weeks), 12.9% in the Lenalidomide arm versus 7.1% in the control arm. On exploratory multivariate analysis, risk factors for early deaths include high tumor burden, MIPI score at diagnosis, and high WBC at baseline (≥ 10 x 109/L).

SIDE EFFECTS Embryo-fetal toxicity, hematologic toxicity, venous and arterial thromboembolism, increased mortality in patients with CLL, second primary malignancies, hepatotoxicity, allergic reactions, tumor lysis syndrome, tumor flare reactions, impaired stem cell mobilization, thyroid disorders. early mortality in patients with MCL.

Use in Pregnancy: Based on the mechanism of action, Lenalidomide can cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy. Lenalidomide is a thalidomide analogue. Thalidomide is a human teratogen, inducing a high frequency of severe and life-threatening birth defects such as amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia, micropinna, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented and mortality at or shortly after birth has been reported in about 40% of infants.
Use in Lactation: There is no information regarding the presence of Lenalidomide in human milk, the effects of Lenalidomide on the breastfed infant, or the effects of Lenalidomide on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed infants from Lenalidomide, advise women not to breastfeed during treatment with Lenalidomide.
Pediatric Use: The safety and effectiveness in pediatric patients have not been established.
OVERDOSE: There is no specific experience in the management of Lenalidomide overdose in patients with MM, MDS, or MCL. In dose-ranging studies in healthy subjects, some were exposed to up to 200 mg (administered 100 mg BID) and in single-dose studies, some subjects were exposed to up to 400 mg. Pruritus, urticaria, rash, and elevated liver transaminases were the primary reported AEs. In clinical trials, the dose-limiting toxicity was neutropenia and thrombocytopenia.
PHARMACEUTICAL INFORMATION
Storage: Store below 30° C in a dry place. Protect from light. Keep out of the reach of children.
Packing: Mylomid-10: Each container contains 28 capsules in a blister pack.
Mylomid-25: Each container contains 21 capsules in a blister pack.

Manufactured by
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