Mylomid

Lenalidomide INN Capsule

DRUG INTERNATIONAL LTD.

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

Table: 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.

ADVERSE EFFECTS

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

CONTRAINDICATIONS

Pregnancy: Lenalidomide can cause fetal harm when administered to a pregnant female. 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.
Severe Hypersensitivity Reactions: Lenalidomide is contraindicated in patients who have demonstrated hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to Lenalidomide.

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. 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.

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 .
Monitor complete blood counts (CBC) in patients taking Lenalidomide for MDS weekly for the first 8 weeks and at least monthly thereafter.
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.
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 24, and then monthly thereafter. Patients may require dose interruption and/or dose reduction.
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. 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). 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: Lenalidomide is not indicated and not recommended for use in CLL outside of controlled clinical trials.
Second Primary Malignancies: 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: 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. 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: Monitor patients at risk closely and take appropriate preventive approaches.
Tumor Flare Reaction: Monitoring and evaluation for TFR is recommended in patients with MCL, FL, or MZL. Tumor flare reaction may mimic progression of disease (PD).
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.
Pediatric Use: The safety and effectiveness in pediatric patients have not been established.
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.
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.
OVERDOSE: There is no specific experience in the management of Lenalidomide overdose in patients with MM, MDS, or MCL.

PHARMACEUTICAL INFORMATION

Storage: Store below 30^{O} C in a dry place. Protect from light. Keep out of the reach of children.
Packing: Mylomid-10: Each box contains 28 capsules in alu-alu blister pack.
Mylomid-25: Each box contains 21 capsules in alu-alu blister pack.