Linamide
Lenalidomide

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

CLINICAL PHARMACOLOGY
Mechanism of Action
Lenalidomide is an analogue of Thalidomide with immunomodulatory, antiangiogenic and antineoplastic properties. Lenalidomide inhibits proliferation and induces apoptosis of certain hematopoietic tumor cells including multiple myeloma, 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 multiple myeloma. Immunomodulatory properties of Lenalidomide include activation of T cells and natural killer (NK) cells, increased numbers of NKT cells, and inhibition of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. In multiple myeloma cells, the combination of Lenalidomide and Dexamethasone synergizes the inhibition of cell proliferation and the induction of apoptosis.

PHARMACODYNAMICS & PHARMACOKINETICS
The effect of Lenalidomide on the QTc interval was evaluated in 60 healthy male subjects in a randomized, thorough QT study with placebo and positive controls. At a dose two times the maximum recommended dose, Lenalidomide does not prolong the QTc interval to any clinically relevant extent. The largest upper bound of the 2-sided 90% CI for the mean differences between Lenalidomide and placebo was below 10 ms.

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.

Distribution: In vitro (14C)-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.

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.

Elimination: Elimination is primarily renal. Following a single oral administration of [14C]-Lenalidomide (25 mg) to healthy subjects, approximately 90% and 4% of the radioactive dose is eliminated within ten days in urine and feces, respectively. Approximately 82% of the radioactive dose is excreted as Lenalidomide in the urine within 24 hours. Hydroxy-Lenalidomide and N-acetyl-Lenalidomide represent 4.59% and 1.83% of the excreted dose, respectively. The renal clearance of Lenalidomide exceeds the glomerular filtration rate. The mean half-life of Lenalidomide is 3 hours in healthy subjects and 3 to 5 hours in patients with MM, MDS or MCL.

INDICATIONS
Linamide is a thalidomide analogue indicated for the treatment of patients with:
- Multiple Myeloma (MM), in combination with Dexamethasone
- Transfusion-dependent anemia due to low- or intermediate-1-risk Myelodysplastic Syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities.
- Mantle Cell Lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included Bortezomib

DOSAGE AND ADMINISTRATION
Multiple Myeloma: The recommended starting dose of Linamide is 25 mg orally once daily on Days 1-21 of repeated 28-day cycles in combination with Dexamethasone.

Myelodysplastic Syndromes: Linamide is indicated for the treatment of 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: The recommended starting dose of Linamide 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.

CONTRAINDICATIONS
Pregnancy
Due to the Lenalidomide's structural similarities to Thalidomide, a known human teratogen, Lenalidomide is contraindicated in females who are pregnant. Lenalidomide is contraindicated in patients who have demonstrated hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to Lenalidomide.

WARNINGS AND PRECAUTIONS
Hematologic Toxicity: Lenalidomide can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q myelodysplastic syndromes had to have a dose delay/reduction during the major study.
Venous and Arterial Thromboembolism: Lenalidomide has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE),as well as risk of myocardial infarction and stroke in patients with multiple myeloma who were treated with Lenalidomide and Dexamethasone therapy.
Hepatic Toxicity: Hepatic failure including fatal cases, has occurred in patients treated with Lenalidomide in combination with Dexamethasone
Allergic Reactions: Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS).
Tumor Lysis Syndrome: Fatal instances of tumor lysis syndrome have been reported during treatment with Lenalidomide. The patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment.
Tumor Flare Reaction: Tumor flare reaction 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.

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.

ADVERSE REACTIONS
Common adverse effects of Lenalidomide are:
Blood and Lymphatic System Disorders: Warm type hemolytic anemia, splenic infarction, bone marrow depression, coagulopathy, hemolysis, hemolytic anemia, refractory anemia
Cardiac Disorders: Cardiac failure congestive, atrial fibrillation, angina pectoris, cardiac arrest, cardiac failure, cardio-respiratory arrest, cardiomyopathy, myocardial infarction, myocardial ischemia, atrial fibrillation aggravated, bradycardia, cardiogenic shock, pulmonary edema, supraventricular arrhythmia, tachyarrhythmia, ventricular dysfunction
Ear and Labyrinth Disorders: Vertigo
Gastrointestinal Disorders: Gastrointestinal hemorrhage, colitis ischemic, intestinal perforation, rectal hemorrhage, colonic polyp, diverticulitis, dysphagia,gastritis,gastroenteritis, gastroesophageal reflux disease, obstructive inguinal hernia, irritable bowel syndrome, melena, pancreatitis due to biliary obstruction, pancreatitis, perirectal abscess, small intestinal obstruction, upper gastrointestinal hemorrhage
Hepatobiliary Disorders: Hyperbilirubinemia, cholecystitis, acute cholecystitis, hepatic failure
Immune System Disorders: Hypersensitivity
Infections and Infestations: Infection bacteremia, central line infection, clostridial infection, ear infection,Enterobacter sepsis, fungal infection,herpes viral infection NOS, influenza, kidney infection
Metabolism and Nutrition Disorders: Dehydration, gout, hypernatremia, hypoglycemia
Musculoskeletal and connective tissue disorders: Arthritis, arthritis aggravated, gouty arthritis, neck pain
Psychiatric Disorders: Confusional state
Respiratory, Thoracic and Mediastinal Disorders: bronchitis, chronic obstructive airways disease exacerbated, respiratory failure, dyspnea exacerbated, interstitial lung disease, lung infiltration, wheezing

PHARMACEUTICAL INFORMATION
Storage Conditions
Store in a cool and dry place, away from light. Keep out of the reach of children.

Presentation & Packaging
Linamide 10 Capsule: Each commercial box contains 3×6's Capsules in Alu-Alu blister pack.
Linamide 25 Capsule: Each commercial box contains 3×6's Capsules in Alu-Alu blister pack.

Manufactured By
BEACON Pharmaceuticals Limited
Mymensingh, Bangladesh

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