Dasanix
Dasatinib

COMPOSITION
Dasanix Tablet: Each film coated tablet contains Dasatinib Monohydrate INN equivalent to Dasatinib 100 mg.

PHARMACOLOGICAL INFORMATION
Mechanism of Action
Dasatinib, at nano molar concentrations, inhibits the following kinases: BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2 and PDGFRβ. Based on modeling studies, Dasatinib is predicted to bind to multiple conformations of the ABL kinase. In vitro, Dasatinib was active in leukemic cell lines representing variants of Imatinib Mesylate sensitive and resistant disease. Dasatinib inhibits the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines overexpressing BCR-ABL. Under the conditions of the assays, Dasatinib was able to overcome Imatinib resistance resulting from BCR-ABL kinase domain mutations, activation of alternate signaling pathways involving the SRC family kinases (LYN, HCK) and multi-drug resistance gene overexpression.

Pharmacokinetics
Absorption
Maximum plasma concentrations (C_{max}) of Dasatinib are observed between 0.5 and 6 hours (T_{max}) following oral administration. Dasatinib exhibits dose proportional increases in AUC and linear elimination characteristics over the dose range of 15 mg to 240 mg/day. The overall mean terminal half-life of Dasatinib is 3 to 5 hours.

Distribution
In patients, Dasatinib has an apparent volume of distribution of 2505L, suggesting that the drug is extensively distributed in the extravascular space. Binding of Dasatinib and its active metabolite to human plasma proteins in vitro was approximately 96% and 93% respectively, with no concentration dependence over the range of 100 to 500 ng/mL.

Metabolism
Dasatinib is extensively metabolized in humans, primarily by the cytochrome P450 enzyme 3A4. CYP3A4 was the primary enzyme responsible for the formation of the active metabolite. Flavin-containing monooxygenase 3 (FMO-3) and uridine diphosphate-glucuronosyltransferase (UGT) enzymes are also involved in the formation of Dasatinib metabolites.

Elimination
Elimination is primarily via the feces. Following a single oral dose of [14C]-labeled Dasatinib, approximately 4% and 85% of the administered radioactivity was recovered in the urine and feces respectively, within 10 days. Unchanged Dasatinib accounted for 0.1% and 19% of the administered dose in urine and feces, respectively, with the remainder of the dose being metabolites.

CLINICAL INFORMATION
Indications
Dasanix is a kinase inhibitor indicated for the treatment of:
- Newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase.
- Adults with chronic, accelerated or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including Imatinib.
- Adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy

Dosage and Administration
The recommended starting dose of Dasatinib for chronic phase CML is 100 mg administered orally once daily. The recommended starting dose of Dasatinib for accelerated phase CML, myeloid or lymphoid blast phase CML or Ph+ ALL is 140 mg administered orally once daily.

Method of Administration
Tablets should not be crushed or cut; they should be swallowed whole. Dasanix can be taken with or without a meal, either in the morning or in the evening.

Use in specific population
- *Nursing Mothers:* Discontinue drug or nursing taking into consideration the importance of the drug to the mother.
- *Hepatic Impairment:* Use Dasanix with caution in patients with hepatic impairment.

Contraindications
Hypersensitivity to the active substance or to any of the excipients.

Warning and Precaution
Myelosuppression
Treatment with Dasanix is associated with severe (NCI CTC Grade 3 or 4) thrombocytopenia, neutropenia and anemia. Their occurrence is more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML.

Bleeding Related Events
In addition to causing thrombocytopenia in human subjects, Dasatinib caused platelet dysfunction in vitro.

Fluid Retention
Dasatinib is associated with fluid retention. In clinical trials, severe fluid retention was reported in up to 10% of patients.

QT Prolongation
Use Dasanix with caution in patients who have or may develop prolongation of the QT interval.
Pulmonary Arterial Hypertension.
Dasanix may increase the risk of developing pulmonary arterial hypertension (PAH) which may occur any time after initiation including after more than one year of treatment.

Embryo-fetal Toxicity
Dasanix can cause fetal harm when administered to a pregnant woman. Adverse fetal and infant outcomes have been reported from women who have taken Dasatinib.

Side Effects
The most common side effects are bloody or black tarry stools, body aches or pain, burning, tingling, numbness or pain in the hands, arms, feet or legs, chest pain, constipation, cough or hoarseness, difficulty with breathing, dizziness, ear congestion, fainting, fast-slow or irregular heartbeat, fever or chills, full or bloated feeling, headache, loss of voice, lower back or side pain, painful or difficult urination.

Drug Interaction
- *CYP3A4 Inhibitors:* May increase Dasatinib drug levels and should be avoided. If coadministration cannot be avoided, monitor closely and consider reducing Dasatinib dose.
- *CYP3A4 Inducers:* May decrease Dasatinib drug levels. If coadministration cannot be avoided, consider increasing Dasatinib dose.
- *Antacids:* May decrease Dasatinib drug levels. Avoid simultaneous administration. If needed, administer the antacid at least 2 hours prior to or 2 hours after the dose of Dasatinib.
- *H_2 Antagonists/Proton Pump Inhibitors:* May decrease Dasatinib drug levels. Consider antacids in place of H_2 antagonists or proton pump inhibitors.

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

Presentation and Packaging
Dasanix Tablet: Each commercial box contains 30 tablets in Alu-Alu blister pack.

LF18001

Manufactured By
BEACON
Pharmaceuticals Limited
Mymensingh, Bangladesh