Leukenib (Imatinib) Innerleaf design

Pantone 185 C & Metallic Coated 8483 C **W - 185 mm X H - 431mm**

Leukenib™
Imatinib

Jenphar Bangladesh | جـنـفـار بنغلاديش

Composition:
Leukenib 100 Tablet: Each film coated tablet contains Imatinib Mesylate INN equivalent to Imatinib 100 mg.
Leukenib 400 Tablet: Each film coated tablet contains Imatinib Mesylate INN equivalent to Imatinib 400 mg.

Pharmacology:
Imatinib mesylate is a protein-tyrosine kinase inhibitor that inhibits the BCR-ABL tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in CML. Imatinib inhibits proliferation and induces apoptosis in BCR-ABL positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia. Imatinib inhibits tumor growth of BCR-ABL transfected murine myeloid cells as well as BCR-ABL positive leukemia lines derived from CML patients in blast crisis. Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-kit, and inhibits PDGF- and SCF-mediated cellular events.

Indications:
Imatinib is a kinase inhibitor indicated for the treatment of:
- Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase.
- Patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) after failure of interferon-alpha therapy.
- Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy.
- Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).
- Adult patients with myelodysplastic / myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements.
- Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown.
- Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown.
- Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).
- Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).
- Adjuvant treatment of adult patients following resection of Kit (CD117) positive GIST.

Dose & administration:
- Adults with Ph+ CML CP: 400 mg/day
- Adults with Ph+ CML AP or BC: 600 mg/day
- Pediatrics with Ph+ CML CP: 340 mg/m²/day
- Adults with Ph+ ALL: 600 mg/day
- Pediatrics with Ph+ ALL: 340 mg/m²/day
- Adults with MDS/MPD: 400 mg/day
- Adults with ASM: 100 mg/day or 400 mg/day
- Adults with HES/CEL: 100 mg/day or 400 mg/day
- Adults with DFSP: 800 mg/day
- Adults with GIST: 400 mg/day
- Patients with mild to moderate hepatic impairment: 400 mg/day
- Patients with severe hepatic impairment: 300 mg/day.

All doses of Imatinib should be taken with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day.

Imatinib can be dissolved in water or apple juice for patients having difficulty swallowing.

Dose Modification Guideline:
Hepatic impairment: Patients with mild and moderate hepatic impairment do not require a dose adjustment and should be treated per the recommended dose. A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment.

Renal impairment: Patients with moderate renal impairment (CrCL=20-39 mL/min) should receive a 50% decrease in the recommended starting dose and increased as tolerated. Doses greater than 600 mg are not recommended in patients with mild renal impairment (CrCL=40-59 mL/min). For patients with moderate renal impairment doses greater than 400 mg are not recommended. Imatinib should be used with caution in patients with severe renal impairment. A dose of 100 mg/day was tolerated in two patients with severe renal impairment.

Contra-indication:
None.

Warning and precaution:
- Fetal harm can occur when administered to a pregnant woman. Women should be apprised of the potential harm to the fetus.
- Edema and severe fluid retention have occurred. Weigh patients regularly and manage unexpected rapid weight gain by drug interruption and diuretics.
- Cytopenias, particularly anemia, neutropenia, and thrombocytopenia, have occurred. Manage with dose reduction or dose interruption and in rare cases discontinuation of treatment. Perform complete blood counts weekly for the first month, biweekly for the second month, and periodically thereafter.
- Severe congestive heart failure and left ventricular dysfunction have been reported, particularly in patients with comorbidities and risk factors. Patients with cardiac disease or risk factors for cardiac failure should be monitored and treated.
- Severe hepatotoxicity may occur. Assess liver function before initiation of treatment and monthly thereafter or as clinically indicated. Monitor liver function when combined with chemotherapy known to be associated with liver dysfunction.
- Grade 3/4 hemorrhage has been reported in clinical studies in patients with newly diagnosed CML and with GIST. GI tumor sites may be the source of GI bleeds in GIST.
- Gastrointestinal perforations, some fatal, have been reported.
- Cardiogenic shock/left ventricular dysfunction has been associated with the initiation of Imatinib in patients with conditions associated with high eosinophil levels (e.g., HES, MDS/MPD and ASM).
- Hypothyroidism has been reported in thyroidectomy patients undergoing levothyroxine replacement. Closely monitor TSH levels in such patients.
- Consider potential toxicities, specifically, liver, kidney, and cardiac toxicity, and immunosuppression from long-term use.
- Tumor lysis syndrome. Close monitoring is recommended.

Side effects:
The most frequently reported adverse reactions (greater than or equal to 30%) were edema, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue and abdominal pain.

Use in pregnancy & lactation:
Pregnancy: Pregnancy Category D. Imatinib can cause fetal harm when administered to a pregnant woman.

Nursing Mothers: Imatinib mesylate or its metabolites are excreted in human milk. In nursing infants from Imatinib, nursing should be discontinued.

Use in children & adolescents:
Pediatric Use: Imatinib safety and efficacy have been demonstrated in children with newly diagnosed Ph+ chronic phase CML and Ph+ ALL. There are no data in children under 1 years of age.

Geriatric Use: No difference was observed in the safety profile in patients older than 65 years as compared to younger patients, with the exception of a higher frequency of edema. The efficacy of Imatinib was similar in older and younger patients.

Drug interaction:
Agents Inducing CYP3A Metabolism: Pretreatment of healthy volunteers with multiple doses of rifampin followed by a single dose of Imatinib, increased Imatinib oral-dose clearance by 3.8-fold, which significantly ($p<0.05$) decreased mean Cmax and AUC. If alternative treatment cannot be administered, a dose adjustment should be considered.

Agents Inhibiting CYP3A Metabolism: There was a significant increase in exposure to Imatinib (mean Cmax and AUC increased by 26% and 40%, respectively) in healthy subjects when Imatinib was co-administered with a single dose of ketoconazole (a CYP3A4 inhibitor). Caution is recommended when administering Imatinib with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole). Grapefruit juice may also increase plasma concentrations of imatinib and should be avoided.

Interactions with Drugs Metabolized by CYP3A4: Imatinib increases the mean Cmax and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5-fold, respectively, suggesting an inhibition of the CYP3A4 by Imatinib. Particular caution is recommended when administering Imatinib with CYP3A4 substrates that have a narrow therapeutic window (e.g., alfentanil, cyclosporine, diergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus or tacrolimus). Imatinib will increase plasma concentration of other CYP3A4 metabolized drugs (e.g., triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.). Patients who require anticoagulation should receive low-molecular weight or standard heparin instead of warfarin.

Interactions with Drugs Metabolized by CYP2D6: No specific studies have been performed and caution is recommended. No dose adjustment is necessary.

Interaction with Acetaminophen: No specific studies in humans have been performed and caution is recommended.

Overdose:
Experience with doses greater than 800 mg is limited. Isolated cases of Imatinib overdose have been reported. In the event of overdose, the patient should be observed and appropriate supportive treatment given.

Storage:
Store in a cool & dry place below 30°C, protect from light. Keep out of the reach of children.

Packing:
Leukenib 100 Tablet: Each box contains 30 film coated tablets and one packet silica gel in a sealed HDPE container.
Leukenib 400 Tablet: Each box contains 30 film coated tablets and one packet silica gel in a sealed HDPE container.

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Manufactured by:
Jenphar Bangladesh Ltd.
Sreepur, Gazipur, Bangladesh.