Treat your blood
precisely

Ibrutix

Ibrutinib 140 mg capsule

Ibrutinib is a potent inhibitor of Bruton's Tyrosine Kinase (BTK), which is an essential component of B-cell receptor signaling, that promotes the survival and proliferation of Chronic Lymphocytic Leukemia (CLL) cells.

BEACON Pharma introduces,

Ibrutix

Ibrutinib 140 mg capsule

Trusted choice for lymphoma

Demonstrated high response rates and prolonged progression-free survival (PFS) in CLL at 26 months

75% of Ibrutinib treated patients

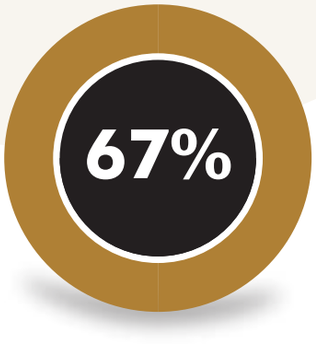
Without progression at **26** months

83% of Ibrutinib treated patients

Survival beyond at **26** months

Ibrutinib, an oral inhibitor of BTK, is approved for patients with Mantle Cell Lymphoma (MCL) who have received one prior therapy.

Demonstrated significant overall response in Mantle Cell Lymphoma (MCL)



Overall Response Rate (ORR)

Durable remission ensured

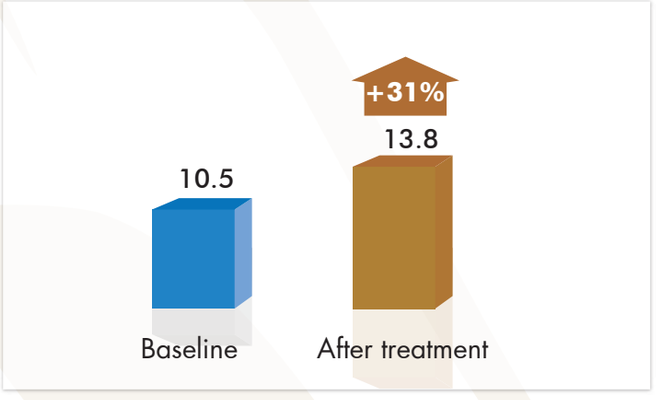
Ibrutinib is highly active with durable response and safe in pre-treated patients with Waldenstrom Macroglobulinemia (WM).

Ibrutix

Ibrutinib 140 mg capsule

Trusted choice for lymphoma

Increase the haemoglobin level in WM patients



Shows significant rate in progression free survival and overall survival

Greater response assured

Recommended daily dose for **WM & CLL**

1 Once Daily

Recommended daily dose for **MCL**

1 Once Daily

Ibrutix

Ibrutinib 140 mg capsule

Trusted choice for lymphoma

- Advanced option for Chronic Lymphocytic Leukemia (CLL)
- Significant Outcome in Waldenstrom Macroglobulinemia (WM) & Mantle Cell Lymphoma (MCL)
- Once daily oral dose

Abridged Prescribing Information

COMPOSITION: ***Ibrutix Capsule:*** Each capsule contains Ibrutinib INN 140 mg. **CLINICAL PHARMACOLOGY:** ***Mechanism of Action:*** Ibrutinib is a small-molecule inhibitor of BTK. Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that Ibrutinib inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro. **Pharmacodynamics:** In patients with recurrent B-cell lymphoma > 90% occupancy of the BTK active site in peripheral blood mononuclear cells was observed up to 24 hours after Ibrutinib doses of ≥2.5 mg/kg/day (≥175 mg/day for average weight of 70 kg). In healthy subjects, at a single dose 3 times the maximum recommended dose (1680 mg), Ibrutinib did not prolong the QT interval to any clinically relevant extent. **Pharmacokinetics:** ***Absorption:*** Ibrutinib is absorbed after oral administration with a median Tmax of 1 to 2 hours. Ibrutinib exposure increases with doses up to 840 mg. The steady-state AUC (mean ± standard deviation) observed in patients at 560 mg is 953 ± 705 ng.h/mL and in patients at 420 mg is 680 ± 517 ng.h/mL. Absolute bioavailability in fasted condition (n = 8) was 2.9% (90% CI = 2.1 – 3.9) and doubled when combined with a meal. Administration with food increased Ibrutinib Cmax and AUC by approximately 2 to 4- and 2-fold, respectively, compared with administration of Ibrutinib after overnight fasting. ***Distribution:*** Reversible binding of Ibrutinib to human plasma protein in vitro was 97.3% with no concentration dependence in the range of 50 to 1000 ng/mL. The volume of distribution (V_d) was 683 L, and the apparent volume of distribution at steady state (V_{d_ss}/F) was approximately 10000 L. ***Metabolism:*** Metabolism is the main route of elimination for Ibrutinib. It is metabolized to several metabolites primarily by cytochrome P450, CYP3A, and to a minor extent by CYP2D6. The active metabolite, PCI-45227, is a dihydrodiol metabolite with inhibitory activity towards BTK approximately 15 times lower than that of Ibrutinib. The range of the mean metabolite to parent ratio for PCI-45227 at steady-state is 1 to 2.8. ***Elimination:*** Intravenous clearance was 62 and 76 L/h in fasted and fed conditions, respectively. In line with the high first-pass effect, the apparent oral clearance is approximately 2000 and 1000 L/h in fasted and fed conditions, respectively. The half-life of Ibrutinib is 4 to 6 hours. Ibrutinib, mainly in the form of metabolites, is eliminated primarily via feces. After a single oral administration of radiolabeled [^{14}C]-Ibrutinib in healthy subjects, approximately 90% of radioactivity was excreted within 168 hours, with the majority (80%) excreted in the feces and less than 10% accounted for in urine. Unchanged Ibrutinib accounted for approximately 1% of the radiolabeled excretion product in feces and none in urine, with the remainder of the dose being metabolites. ***Age:*** In older patients (67 to 81 years), there is a 14% higher Ibrutinib exposure predicted. Dose adjustment by age is not warranted. ***Gender:*** Gender does not alter Ibrutinib systemic clearance. ***Renal Impairment:*** Ibrutinib is not significantly cleared renally; urinary excretion of metabolites is < 10% of the dose. Creatinine clearance (CrCL) > 25 mL/min had no influence on the exposure to Ibrutinib. There are no data in patients with severe renal impairment (CrCL < 25 mL/min) or in patients on dialysis. ***Hepatic Impairment:*** Ibrutinib is metabolized in the liver. In a hepatic impairment trial, a single dose of 140 mg of Ibrutinib was administered in non-cancer subjects. Ibrutinib AUC increased 2.7-, 8.2- and 9.8-fold, respectively, in subjects with mild (n=6), moderate (n=10) and severe (n=8) hepatic impairment relative to subjects with normal liver function. Ibrutinib C_{max} increased 5.2-, 8.8- and 7.0-fold, respectively, in subjects with mild, moderate and severe hepatic impairment relative to subjects with normal liver function. **INDICATIONS:** ***Mantle Cell Lymphoma:*** Ibrutinib is indicated for the treatment of patients with Mantle Cell Lymphoma (MCL) who have received at least one prior therapy. ***Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma:*** Ibrutinib is indicated for the treatment of patients with Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL). ***Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion:*** Ibrutinib is indicated for the treatment of patients with Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) with 17p deletion. ***Waldenstrom's Macroglobulinemia:*** Ibrutinib is indicated for the treatment of patients with Waldenstrom's Macroglobulinemia (WM). ***Marginal Zone Lymphoma:*** Ibrutinib is indicated for the treatment of patients with Marginal Zone Lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy. **DOSAGE AND ADMINISTRATION:** ***Dosing Guidelines:*** Administer Ibrutinib orally once daily at approximately the same time each day. Swallow the capsules whole with water. Do not open, break or chew the capsules. ***Dosage: Mantle Cell Lymphoma and Marginal Zone Lymphoma:*** The recommended dose of Ibrutinib for MCL and MZL is 560 mg (four 140 mg capsules) orally once daily until disease progression or unacceptable toxicity. ***Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma and Waldenstrom's Macroglobulinemia*** The recommended dose of Ibrutinib for CLL/SLL and WM is 420 mg (three 140 mg capsules) orally once daily until disease progression or unacceptable toxicity. The recommended dose of Ibrutinib for CLL/SLL when used in combination with Bendamustine and Rituximab (administered every 28 days for up to 6 cycles) is 420 mg (three 140 mg capsules) orally once daily until disease progression or unacceptable toxicity. **CONTRAINDICATIONS:** None **WARNINGS AND PRECAUTIONS:** ***Hemorrhage:*** Fatal bleeding events have occurred in patients treated with Ibrutinib. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with Ibrutinib. The mechanism for the bleeding events is not well understood. Ibrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding Ibrutinib for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding. ***Infections***: Fatal and non-fatal infections have occurred with Ibrutinib therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with Ibrutinib. Evaluate patients for fever and infections and treat appropriately. ***Cytopenias:*** Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 13%) based on laboratory measurements occurred in patients treated with single agent Ibrutinib. Monitor complete blood counts monthly. ***Atrial Fibrillation:*** Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with Ibrutinib, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. Atrial fibrillation should be managed appropriately, and if it persists, consider the risks and benefits of Ibrutinib treatment and follow dose modification guidelines. ***Hypertension:*** Hypertension (range, 6 to 17%) has occurred in patients treated with Ibrutinib with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting Ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate. ***Second Primary Malignancies:*** Other malignancies (range, 3 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with Ibrutinib. The most frequent second primary malignancy was non-melanoma skin cancer (range, 2 to 13%). ***Tumor Lysis Syndrome:*** Tumor lysis syndrome has been infrequently reported with Ibrutinib therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate. ***Embryo-Fetal Toxicity:*** Based on findings in animals, Ibrutinib can cause fetal harm when administered to a pregnant woman. Administration of Ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryofetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with hematologic malignancies. Advise women to avoid becoming pregnant while taking Ibrutinib and for 1 month after cessation of therapy. 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 hazard to a fetus. **PHARMACEUTICAL INFORMATION:** ***Storage Conditions:*** Store in a cool and dry place, away from light. Keep out of the reach of children. ***Presentation & Packaging: Ibrutix Capsule:*** Each commercial box contains 120 Capsules in a bottle.

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Light for life