Butinib

Ibrutinib INN

DRUG INTERNATIONAL LTD.

Composition: Each capsule contains Ibrutinib INN 140 mg.

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).

Pharmacokinetics:

Absorption: Absolute bioavailability of Ibrutinib in fasted condition was 2.9% (90% CI: 2.1, 3.9) in healthy subjects. Ibrutinib is absorbed after oral administration with a median Tmax of 1 hour to 2 hours.

Distribution: Reversible binding of Ibrutinib to human plasma protein in vitro was 97.3% with no concentration dependence in the range of 50 ng/mL to 1000 ng/mL. The volume of distribution (Vd) was 683 L, and the apparent volume of distribution at steady state (Vd,ss/F) was approximately 10,000 L.

Elimination: Intravenous clearance was 62 L/h in fasted conditions and 76 L/h in fed conditions. In line with the high first-pass effect, the apparent oral clearance is 2000 L/h in fasted conditions and 1000 L/h in fed conditions. The half-life of Ibrutinib is 4 hours to 6 hours.

Metabolism: Ibrutinib is metabolized to several metabolites primarily by cytochrome P450 (CYP) 3A 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.

Excretion: Ibrutinib, mainly in the form of metabolites, is eliminated primarily via feces. After a single oral administration of radiolabeled ibrutinib, 90% of radioactivity was excreted within 168 hours, with 80% excreted in the feces and less than 10% eliminated in urine. Unchanged Ibrutinib accounted for 1% of the radiolabeled excreted dose in feces and none in urine, with the remainder of the excreted dose being metabolites.

Indications:

Mantle Cell Lymphoma: Butinib is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Butinib is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p Deletion: Butinib is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion.

Waldenström's Macroglobulinemia: Butinib is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

Marginal Zone Lymphoma: Butinib is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.

Dosage and Administration:

Mantle Cell Lymphoma and Marginal Zone Lymphoma: The recommended dose of Butinib for MCL and MZL is 560 mg orally once daily until disease progression or unacceptable toxicity.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma and Waldenström's Macroglobulinemia: The recommended dose of Butinib for CLL/SLL and WM as a single agent, in combination with Rituximab for WM, or in combination with Bendamustine and Rituximab for CLL/SLL is 420 mg orally once daily until disease progression or unacceptable toxicity. When administering Butinib in combination with Rituximab, it should be administered prior to Rituximab when given on the same day.

Chronic Graft versus Host Disease: The recommended dose of Butinib for cGVHD is 420 mg orally once daily until cGVHD progression, recurrence of an underlying malignancy, or unacceptable toxicity. When a patient no longer requires therapy for the treatment of cGVHD, Butinib should be discontinued considering the medical assessment of the individual patient.

Dose Modification:

Toxicity Occurrence	Dose Modification for MCL and MZL After Recovery Starting Dose = 560 mg	Dose Modification for CLL/SLL, WM, and cGVHD After Recovery Starting Dose = 420 mg
First	Restart at 560 mg daily	Restart at 420 mg daily
Second	Restart at 420 mg daily	Restart at 280 mg daily
Third	Restart at 280 mg daily	Restart at 140 mg daily
Fourth	Discontinue Butinib	Discontinue Butinib

Or, as directed by the registered physicians.

Side Effects:

- Hemorrhage
- Infections
- Cytopenias
- Cardiac Arrhythmias
- Hypertension
- Second Primary Malignancies
- Tumor Lysis Syndrome

Contraindication: It is contraindicated in patients with known hypersensitivity to Ibrutinib or any other components of this product.

Use in Pregnancy and Lactation: There are no available data on Butinib use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. If Butinib is used during pregnancy or if the patient becomes pregnant while taking Butinib, the patient should be apprised of the potential hazard to the fetus.

Lactation: There is no information regarding the presence of Ibrutinib or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

Contraception: Females: Females of reproductive potential should be advised to avoid pregnancy while taking Butinib and for up to 1 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus. Males: Men should be advised to avoid fathering a child while receiving Butinib, and for 1 month following the last dose of Butinib.

Pediatric Use: The safety and effectiveness of Butinib in pediatric patients has not been established. Pediatric studies have not been completed.

Drug Interactions:

Effect of CYP3A Inhibitors on Ibrutinib: The coadministration of Butinib with a strong or moderate CYP3A inhibitor may increase ibrutinib plasma concentrations. Increased Ibrutinib concentrations may increase the risk of drug-related toxicity. Dose modifications of Butinib are recommended when used concomitantly with Posaconazole, Voriconazole and moderate CYP3A inhibitors. Concomitant use of other strong CYP3A inhibitors should be avoided. Butinib should be interrupted if these inhibitors will be used short-term (such as anti-infectives for seven days or less). Grapefruit and Seville oranges should be avoided during Butinib treatment, as these contain strong or moderate inhibitors of CYP3A.

Effect of CYP3A Inducers on Ibrutinib: The coadministration of Butinib with strong CYP3A inducers may decrease ibrutinib concentrations. Coadministration with strong CYP3A inducers should be avoided.

Precautions:

Hemorrhage: Fatal bleeding events have occurred in patients treated with Butinib. Grade 3 or higher bleeding events (intracranial hemorrhage (including subdural hematoma), gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in 3% of patients, with fatalities occurring in 0.3% of 1,011 patients exposed to Butinib in clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 44% of patients treated with Butinib. Butinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. The benefit-risk should be considered of withholding Butinib for at least 3 to 7 days pre and postsurgery depending upon the type of surgery and the risk of bleeding.

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with Butinib therapy. Grade 3 or greater infections occurred in 24% of 1,011 patients exposed to Butinib in clinical trials. Cases of progressive multifocal leukoencephalopathy (PML) and Pneumocystis jirovecii pneumonia (PJP) have occurred in patients treated with Butinib. Prophylaxis should be considered according to standard of care in patients who are at increased risk for opportunistic infections. Patients should be monitored and evaluated for fever and infections and treated appropriately.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (23%), thrombocytopenia (8%), and anemia (3%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent Butinib. Complete blood counts should be monitored monthly.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with Butinib therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,011 patients exposed to Butinib inclinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias. Periodically patients should be monitored clinically for cardiac arrhythmias.

Hypertension: Hypertension has occurred in 12% of 1,011 patients treated with Butinib in clinical trials with a median time to onset of 5 months (range, 0.03 to 22 months). Patients should be monitored for new onset hypertension or hypertension that is not adequately controlled after starting Butinib. Existing anti-hypertensive medications should be adjusted and/or initiated anti-hypertensive treatment as appropriate.

Second Primary Malignancies: Other malignancies (9%) including non-skin carcinomas (2%) have occurred in 1,011 patients treated with Butinib in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with Butinib therapy. The baseline risk should be assessed (e.g., high tumor burden) and taken appropriate precautions, monitored patients closely and treated as appropriate.

Embryo-Fetal Toxicity: Butinib can cause fetal harm when administered to a pregnant woman. Women should be advised to avoid becoming pregnant while taking Butinib 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.

Overdose: There is no specific experience in the management of Ibrutinib overdose in patients. Patients should be closely monitored who ingest more than the recommended dosage and provided appropriate supportive treatment.

Storage: Store below 30°C in a dry place, away from sunlight. Keep out of the reach of children.

Packing: Each container contains 112 capsules in a box.