Ibrutix
Ibrutinib

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.

Drug Interactions

Co-administration of Ibrutinib with CYP3A Inhibitors

In a sequential design trial of 18 healthy, fasted volunteers, a single dose of 120 mg of Ibrutinib was administered alone on Day 1 and a single dose of 40 mg of Ibrutinib was administered on Day 7 in combination with 400 mg of Ketoconazole (given daily on Days 4 - 9). Ketoconazole increased Ibrutinib dose-normalized Cmax and AUC 29-fold and 24-fold, respectively. Simulations using fasted conditions indicate that moderate CYP3A inhibitors Diltiazem and Erythromycin may increase AUC of Ibrutinib by 5- to 8-fold.

Co-administration of Ibrutinib with CYP3A Inducers

PK data from a dedicated drug interaction trial showed that Rifampin (a strong CYP3A inducer) decreases Ibrutinib C_{max} and AUC by more than 13- and 10-fold. Simulations using PBPK suggested that a moderate CYP3A inducer (Efavirenz) may decrease the AUC of Ibrutinib by up to 3-fold.

Co-administration of Ibrutinib with CYP Substrates

In vitro studies indicated that Ibrutinib (I/Ki < 0.07 using mean C_{max} at 560 mg) and PCI-45227 (I/Ki < 0.03) are unlikely to be inhibitors of any major CYPs at clinical doses. Both Ibrutinib and the PCI-45227 are weak inducers of CYP450 isoenzymes in vitro.

Co-administration of Ibrutinib with Substrates of Transporters

In vitro studies indicated that Ibrutinib is not a substrate of P-gp (p-glycoprotein) or BCRP (breast cancer resistance protein) transporters but is an in vitro inhibitor of P-gp and BCRP. Systemic Ibrutinib is unlikely to be an inhibitor of P-gp at clinical doses ($[I]_1$/Ki < 0.1) but may inhibit BCRP. Ibrutinib may have an effect on P-gp or BCRP substrates in the GI tract due to higher local concentrations after an oral dose. Co-administration of oral narrow therapeutic index P-gp or BCRP substrates (e.g., Digoxin, Methotrexate) with Ibrutinib may increase their blood concentration.

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.

Dose Modifications for Adverse Reactions

Interrupt Ibrutinib therapy for any Grade 3 or greater non-hematological toxicities, Grade 3 or greater neutropenia with infection or fever, or Grade 4 hematological toxicities. Once the symptoms of the toxicity have resolved to Grade 1 or baseline (recovery), Ibrutinib therapy may be reinitiated at the starting dose. If the toxicity reoccurs, reduce dose by one capsule (140 mg per day). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue Ibrutinib.

Recommended dose modifications are described below:

Toxicity Occurrence	MCL and MZL Dose Modification After Recovery Starting Dose = 560 mg	CLL/SLL and WM Dose Modification 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 Ibrutinib	Discontinue Ibrutinib

Dose Modifications for Use with CYP3A Inhibitors

Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

Concomitant use of strong CYP3A inhibitors which would be taken chronically (e.g., Ritonavir, Indinavir, Nelfinavir, Saquinavir, Boceprevir, Telaprevir, Nefazodone) is not recommended. For short-term use (treatment for 7 days or less) of strong CYP3A inhibitors (e.g., Antifungals and antibiotics) consider interrupting Ibrutinib therapy until the CYP3A inhibitor is no longer needed.

Reduce Ibrutinib dose to 140 mg if a moderate CYP3A inhibitor must be used (e.g., Fluconazole, Darunavir, Erythromycin, Diltiazem, Atazanavir, Aprepitant, Amprenavir, Fosamprenavir, Crizotinib, Imatinib, Verapamil, and Ciprofloxacin).

Patients taking concomitant strong or moderate CYP3A inhibitors should be monitored more closely for signs of Ibrutinib toxicity.

Dose Modifications for Use in Hepatic Impairment

For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 140 mg daily (one capsule). Avoid the use of Ibrutinib in patients with moderate or severe hepatic impairment (Child-Pugh classes B and C).

Missed Dose

If a dose of Ibrutinib is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra capsules of Ibrutinib should not be taken to make up for the missed dose.

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.

ADVERSE REACTIONS

The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia, thrombocytopenia, diarrhea, anemia, musculoskeletal pain, rash, nausea, bruising, fatigue, hemorrhage, and pyrexia.

DRUG INTERACTIONS

CYP3A Inhibitors

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A (CYP3A). In healthy volunteers, co-administration of Ketoconazole, a strong CYP3A inhibitor, increased C_{max} and AUC of Ibrutinib by 29- and 24-fold, respectively. The highest Ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of 1445 ± 869 ng.hr/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg).

Avoid concomitant administration of Ibrutinib with strong or moderate inhibitors of CYP3A. For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., Ketoconazole, Itraconazole, Voriconazole, Posaconazole, Clarithromycin, Telithromycin) consider interrupting Ibrutinib therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically. If a moderate CYP3A inhibitor must be used, reduce the Ibrutinib dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of Ibrutinib toxicity.

Avoid grapefruit and Seville oranges during Ibrutinib treatment, as these contain moderate inhibitors of CYP3A.

CYP3A Inducers

Administration of Ibrutinib with Rifampin, a strong CYP3A inducer, decreased Ibrutinib C_{max} and AUC by approximately 13- and 10-fold, respectively.

Avoid concomitant use of strong CYP3A inducers (e.g., Carbamazepine, Rifampin, Phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

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.

Manufactured By
BEACON®
Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

Only for Export

For more info:

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