Ibruxen

Ibrutinib 140 mg

Everest

COMPOSITION

Ibruxen Capsule: Each capsule contains Ibrutinib 140 mg INN.

INDICATIONS AND USAGE

Mantle Cell Lymphoma

Ibrutinib (**Ibruxen**) 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 (**Ibruxen**) 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

Ibrutinib (**Ibruxen**) is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL) with 17p deletion.

Waldenstrom Macroglobulinemia (WM)

Ibrutinib (**Ibruxen**) is indicated for the treatment of patients with Waldenstrom Macroglobulinemia (WM).

Marginal Zone Lymphoma

Ibrutinib (**Ibruxen**) 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.

Chronic Graft versus Host Disease

Ibrutinib (**Ibruxen**) is indicated for the treatment of adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy

DOSAGE AND ADMINISTRATION

Dosing Guidelines

Administer Ibrutinib (**Ibruxen**) orally once daily at approximately the same time each day. Swallow the capsules whole with water. Do not open, break, or chew the capsules.

Recommended Dosage

Mantle Cell Lymphoma and Marginal Zone Lymphoma

The recommended dose of Ibrutinib (**Ibruxen**) 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 Macroglobulinemia (WM)

The recommended dose of Ibrutinib (**Ibruxen**) 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.

Chronic Graft versus Host Disease

The recommended dose of Ibrutinib (**Ibruxen**) for cGVHD is 420 mg (three 140 mg capsules) 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, Ibrutinib should be discontinued considering the medical assessment of the individual patient.

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.

Toxicity Occurrence	MCL and MZL Dose Modification After Recovery Starting Dose=560mg	CLL/SLL and WM Dose Modification After Recovery Starting Dose=420mg
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 Band 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

Hypersensitivity to Ibrutinib or to any of the excipients.

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 (including bacterial, viral, or fungal) 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. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and 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 with B-cell malignancies treated with single agent Ibrutinib. Monitor complete blood counts monthly.

Cardiac Arrhythmias

Fatal and serious cardiac arrhythmias have occurred with Ibrutinib therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0 to 1% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 0 to 6% of patients. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias. Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias 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 embryo-fetal 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 following adverse reactions are discussed in more detail in other sections of the labeling: Hemorrhage, Infections, Cytopenias, Atrial Fibrillation, Hypertension, Second Primary Malignancies and Tumor Lysis Syndrome.

The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite. The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

DRUG INTERACTIONS

Effect of CYP3A Inhibitors on Ibrutinib

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A (CYP3A). In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased Cmax 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 grape fruit and Seville oranges during Ibrutinib treatment, as these contain moderate inhibitors of CYP3A.

Effect of CYP3A Inducers on Ibrutinib

Administration of Ibrutinib with rifampin, a strong CYP3A inducer, decreased Ibrutinib Cmax and AUC by approximately 13 & 10 fold, respectively. Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John'sWort). Consider alternative agents with less CYP3A induction.

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USE IN SPECIFIC POPULATIONS

Pregnancy

Ibrutinib, a kinase inhibitor, can cause fetal harm based on findings from animal studies. In animal reproduction studies, administration of Ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including malformations. If Ibrutinib is used during pregnancy or if the patient becomes pregnant while taking Ibrutinib, the patient should be apprised of the potential hazard to the fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Lactation

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

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating Ibrutinib therapy.

Contraception

Females

Advise females of reproductive potential to avoid pregnancy while taking Ibrutinib 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

Advise men to avoid fathering a child while receiving Ibrutinib, and for 1 month following the last dose of Ibrutinib.

Pediatric Use

The safety and effectiveness of Ibrutinib in pediatric patients has not been established.

Geriatric Use

Of the 905 patients in clinical studies of Ibrutinib, 62% were ≥ 65 years of age, while 21% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades) and Grade 3 or higher pneumonia occurred more frequently among older patients treated with Ibrutinib.

Hepatic Impairment

Ibrutinib is metabolized in the liver. In a hepatic impairment study, data showed an increase in Ibrutinib exposure. The safety of Ibrutinib has not been evaluated in cancer patients with mild to severe hepatic impairment by Child-Pugh criteria. Monitor patients for signs of Ibrutinib toxicity and follow dose modification guidance as needed. It is not recommended to administer Ibrutinib to patients with moderate or severe hepatic impairment.

Plasmapheresis

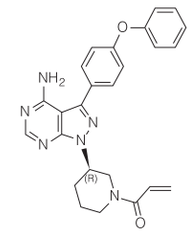
Management of hyperviscosity in WM patients may include plasmapheresis before and during treatment with Ibrutinib. Modifications to Ibrutinib dosing are not required.

OVERDOSAGE

There is no specific experience in the management of Ibrutinib over dose in patients. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Closely monitor patients who ingest more than the recommended dosage and provide appropriate supportive treatment.

DESCRIPTION

Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK). It is a white to off-white solid with the empirical formula $C_{25}H_{24}N_6O_2$ and a molecular weight 440.50. Ibrutinib is freely soluble in dimethyl sulfoxide, soluble in methanol and practically insoluble in water. The chemical name for ibrutinib is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one and has the following structure:



Ibruxen (Ibrutinib) capsules for oral administration are available in 140 mg capsule. Each capsule contains Ibrutinib (active ingredient) and required inactive pharmaceuticals excipients.

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).

At a single dose 3 times the maximum recommended dose (1680 mg), Ibrutinib did not prolong the QT interval to any clinically relevant extent.

In vitro Platelet Aggregation

Ibrutinib demonstrated inhibition of collagen-induced platelet aggregation, with IC50 values at 4.6μM (2026ng/mL), 0.8μM (352ng/mL), and 3μM (1321ng/mL) in blood samples from healthy donors, donors taking warfarin, and donors with severe renal dysfunction, respectively. Ibrutinib did not show meaningful inhibition of platelet aggregation for ADP, arachidonic acid, ristocetin, and TRAP-6.

Pharmacokinetics

Ibrutinib exposure increases with doses up to 840 mg (1.5 times the maximum approved recommended dosage) in patients with B-cell malignancies. The mean steady-state AUC (% coefficient of variation) observed in patients at 560 mg with MCL is 865 (69%) ng.h/mL and with MZL is 978 (82%) ng.h/mL, and in patients at 420 mg with CLL/SLL is 708 (71%) ng.h/mL, with WM is 324 (48%) ng.h/mL, and with cGVHD is 1159 (50%) ng.h/mL. Steady-state concentrations of ibrutinib without CYP3A inhibitors were achieved with an accumulation ratio of 1 to 1.6 after 1 week of multiple daily doses of 420 mg or 560 mg.

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 T_{max} of 1 hour to 2 hours. The administration of Ibrutinib with a high-fat and high-calorie meal (800 calories to 1,000 calories with approximately 50% of total caloric content of the meal from fat) increased Ibrutinib C_{max} by 2- to 4-fold and AUC by approximately 2-fold, compared with administration of Ibrutinib after overnight fasting. *In vitro* studies suggest that Ibrutinib is not a substrate of p-glycoprotein (P-gp) or breast cancer resistance protein (BCRP).

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 (V_d) was 683 L, and the apparent volume of distribution at steady state ($V_{d,ss}$/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

Metabolism is the main route of elimination for Ibrutinib. It 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.

Specific Populations

Age and Sex

Age and sex have no clinically meaningful effect on Ibrutinib pharmacokinetics.

Patients with Renal Impairment

Mild and moderate renal impairment (creatinine clearance [CLcr] > 25 mL/min as estimated by Cockcroft-Gault equation) had no influence on the exposure of Ibrutinib. No data is available in patients with severe renal impairment (CLcr < 25 mL/min) or in patients on dialysis.

Patients with Hepatic Impairment

The AUC of Ibrutinib increased 2.7-fold in subjects with mild hepatic impairment (Child-Pugh class A), 8.2-fold in subjects with moderate hepatic impairment (Child-Pugh class B) and 9.8-fold in subjects with severe hepatic impairment (Child-Pugh class C) relative to subjects with normal liver function. The C_{max} of Ibrutinib increased 5.2-fold in mild hepatic impairment, 8.8-fold in moderate hepatic impairment and 7-fold in severe hepatic impairment relative to subjects with normal liver function.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ibrutinib. Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an *in vivo* bone marrow micronucleus assay in mice at doses up to 2000 mg/kg. Rats were administered oral daily doses of ibrutinib for 4 weeks prior to pairing and during pairing in males and 2 weeks prior to pairing and during pairing in females. Treatment of female rats continued following pregnancy up to gestation day (GD) 7, and treatment of male rats continued until end of study. No effects on fertility or reproductive capacities were observed in male or female rats up to the maximum dose tested, 100 mg/kg/day (Human Equivalent Dose [HED] 16 mg/kg).

PHARMACEUTICAL INFORMATION

Storage Conditions

Store **Ibruxen** between 20°C and 25°C (68°F and 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F), protect from light.

Keep **Ibruxen** out of the reach and sight of children.

Dispensed only in original container and do not use if seal over bottle opening is broken or missing.

HOW SUPPLIED

Ibruxen Capsule: Each child-resistant HDPE container contains 120 capsules and one packet silica gel.

Manufactured By
Everest Pharmaceuticals Ltd.
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