Ibrunib
Ibrutinib

Julphar Bangladesh | جلفار بنغلاديش

Composition:
Ibrunib Capsule: Each capsule contains Ibrutinib INN 140 mg.

Description:
Ibrutinib is an inhibitor of Bruton's Tyrosinekinase (BTK). It is a white to off-white solid with the empirical formula $C_{25}H_{24}N_8O_2$ 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. Ibrunib capsules for oral administration are supplied as white opaque capsules that contain 140 mg Ibrutinib as the active ingredient. Each capsule also contains the following inactive ingredients: Microcrystalline Cellulose, Croscarmellose Sodium, Sodium Lauryl Sulfate and Magnesium Stearate. Each white opaque capsule is marked with "Ibrutinib 140 mg".

Indications and Usage:
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.
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion
Ibrutinib is indicated for the treatment of patients with chronic lymphocytic leukemia.
Waldenstrom Macroglobulinemia (WM)
Ibrutinib is indicated for the treatment of patients with Waldenstrom 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-CD 20-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 Macroglobulinemia (WM)
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.

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 are turn 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 the active substance or to any of the excipients.

Drug Interaction:
CYP3A Inhibitors
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.
CYP3A Inducers
Administration of Ibrutinib with rifampin, astrong 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.

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 hyper viscosity in WM patients may include plasmapheresis before and during treatment with Ibrutinib. Modifications to Ibrutinib dosing are not required.

Undesirable Effects:
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.
Additional Important Adverse Reactions: Diarrhea, Visual Disturbance.

Over Dose:
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.

Pharmaceutical Information:
Storage Condition
Store in a dry place below 30° C, protect from light. Keep out of the reach of children.
How Supplied
Ibrunib 140 Capsule: Each box contains 120 capsules and one packet silica gel in a sealed plastic container.

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

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