Acalanib

Acalabrutinib
INN 100 mg Capsule

DRUG INTERNATIONAL LTD.

Composition: Each capsule contains Acalabrutinib INN 100 mg.

Mechanism of Action: Acalabrutinib is a small-molecule inhibitor of BTK. Acalabrutinib and its active metabolite, ACP-5862, form 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. In B cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. In nonclinical studies, Acalabrutinib inhibited BTK-mediated activation of downstream signaling proteins CD86 and CD69 and inhibited malignant B-cell proliferation and tumor growth in mouse xenograft models.

Pharmacokinetics:

Absorption: The geometric mean absolute bioavailability of Acalabrutinib was 25%. Median [min, max] time to peak Acalabrutinib plasma concentrations (Tmax) was 0.9 [0.5, 1.9] hours, and 1.6 [0.9, 2.7] hour for ACP-5862.

Distribution: Reversible binding to human plasma protein was 97.5% for Acalabrutinib and 98.6% for ACP-5862. The in vitro mean blood-to-plasma ratio was 0.8 for Acalabrutinib and 0.7 for ACP-5862. The geometric mean (% CV) steady-state volume of distribution (Vss) was approximately 101 (52%) L for Acalabrutinib and 67 (32%) L for ACP-5862.

Elimination: The geometric mean (% CV) terminal elimination half-life (t½) was 1 (59%) hour for Acalabrutinib and 3.5 (24%) hours for ACP-5862. The geometric mean (%CV) apparent oral clearance (CL/F) was 71 (35%) L/hr for Acalabrutinib and 13 (42%) L/hr for ACP-5862.

Metabolism: Acalabrutinib is predominantly metabolized by CYP3A enzymes, and to a minor extent, by glutathione conjugation and amide hydrolysis, based on in vitro studies. ACP-5862 was identified as the major active metabolite in plasma with a geometric mean exposure (AUC) that was approximately 2-to 3-fold higher than the exposure of Acalabrutinib. ACP-5862 is approximately 50% less potent than Acalabrutinib with regard to BTK inhibition.

Excretion: Following administration of a single 100 mg radiolabeled Acalabrutinib dose in healthy subjects, 84% of the dose was recovered in the feces and 12% of the dose was recovered in the urine, with less than 2% of the dose excreted as unchanged Acalabrutinib in urine and feces.

Indications:

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

This indication is approved under accelerated approval based on overall response rate approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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

Dosage and Administration:

Acalabrutinib as Monotherapy: For patients with MCL, CLL, or SLL, the recommended dose of Acalabrutinib is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity.

Acalabrutinib in Combination with Obinutuzumab: For patients with previously untreated CLL or SLL, the recommended dose of Acalabrutinib is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity. Start Acalabrutinib at Cycle 1 (each cycle is 28 days). Start Obinutuzumab at Cycle 2 for a total of 6 cycles and refer to the Obinutuzumab prescribing information for recommended dosing. Administer Acalabrutinib prior to Obinutuzumab when given on the same day.

Advise patients to swallow capsule whole with water. Advise patients not to open, break or chew the capsules. Acalabrutinib may be taken with or without food. If a dose of Acalabrutinib is missed by more than 3 hours, it should be skipped and the next dose should be taken at its regularly scheduled time. Extra capsules of Acalabrutinib should not be taken to make up for a missed dose.

Recommended Dosage for Hepatic Impairment: Avoid administration of Acalabrutinib in patients with severe hepatic impairment. Dose modifications are not required for patients with mild or moderate hepatic impairment.

Recommended Dose Modifications for Use with CYP3A Inhibitors or Inducers

CYP3A	Co-administered Drug	Recommended Acalabrutinib use
Inhibition	Strong CYP3A inhibitor	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for up to seven days), interrupt Acalabrutinib.
	Moderate CYP3A inhibitor	100 mg once daily.
Induction	Strong CYP3A inducer	Avoid concomitant use. If these inducers cannot be avoided, increase Acalabrutinib dose to 200 mg approximately every 12 hours.

Concomitant Use with Gastric Acid Reducing Agents:

Proton Pump Inhibitors: Avoid concomitant use.

H2-Receptor Antagonists: Take Acalabrutinib 2 hours before taking a H2-receptor antagonist.

Antacids: Separate dosing by at least 2 hours.

Recommended Dose Modifications for Adverse Reactions

Event	Adverse Reaction Occurrence	Dose Modification (Starting dose = 100 mg approximately every 12 hours)
Grade 3 or greater non-hematologic toxicities, Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia or Grade 4 neutropenia lasting longer than 7 days	First and Second	Interrupt Acalabrutinib. Once toxicity has resolved to Grade or baseline level, Acalabrutinib may be resumed at 100 mg approximately every 12 hours.
	Third	Interrupt Acalabrutinib. Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE may be resumed at a reduced frequency of 100 mg once daily.
	Fourth	Discontinue Acalabrutinib

Or, as directed by the registered physicians.

Side Effects:

• Serious and Opportunistic Infections • Hemorrhage • Cytopenias • Second Primary Malignancies • Atrial Fibrillation and Flutter

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

Use in Pregnancy and Lactation: Acalabrutinib may cause fetal harm and dystocia when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. Pregnant women should be advised of the potential risk to a fetus.

Lactation: No data are available regarding the presence of acalabrutinib or its active metabolite in human milk, its effects on the breastfed child, or on milk production. Acalabrutinib and its active metabolite were present in the milk of lactating rats. Due to the potential for adverse reactions in a breastfed child from Acalabrutinib, lactating women should be advised not to breastfeed while taking Acalabrutinib and for at least 2 weeks after the final dose.

Females and Males of Reproductive Potential:

Pregnancy: Pregnancy testing is recommended for females of reproductive potential prior to initiating Acalabrutinib therapy.

Contraception: Females: Acalabrutinib may cause embryo-fetal harm and dystocia when administered to pregnant women. Female patients of reproductive potential should be advised to use effective contraception during treatment with Acalabrutinib and for at least 1 week following the last dose of Acalabrutinib. 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.

Pediatric Use: The safety and efficacy of Acalabrutinib in pediatric patients have not been established.

Hepatic Impairment: Administration of Acalabrutinib in patients with severe hepatic impairment should be avoided. The safety of Acalabrutinib has not been evaluated in patients with moderate or severe hepatic impairment.

Drug Interactions:

Strong CYP3A Inhibitors		
Clinical Impact	• Co-administration of Acalabrutinib with a strong CYP3A inhibitor (Itraconazole) increased Acalabrutinib plasma concentrations. • Increased Acalabrutinib concentrations may result in increased toxicity.	
Prevention or Management	• Avoid co-administration of strong CYP3A inhibitors with Acalabrutinib. • Alternatively, if the inhibitor will be used short-term, interrupt Acalabrutinib.	
Moderate CYP3A Inhibitors		
Clinical Impact	• Co-administration of Acalabrutinib with a moderate CYP3A inhibitor increased Acalabrutinib plasma concentrations. • Increased Acalabrutinib concentrations may result in increased toxicity.	
Prevention or Management	• Avoid co-administration of strong CYP3A inhibitors with Acalabrutinib. • Alternatively, if the inhibitor will be used short-term, interrupt Acalabrutinib.	
Strong CYP3A Inducers		
Clinical Impact	• Co-administration of Acalabrutinib with a strong CYP3A inducer (Rifampin) decreased Acalabrutinib plasma concentrations. • Decreased Acalabrutinib concentrations may reduce Acalabrutinib activity.	
Prevention or Management	• Avoid co-administration of strong CYP3A inducers with Acalabrutinib. • If a strong CYP3A inducer cannot be avoided, increase the Acalabrutinib dose to 200 mg approximately every 12 hours.	
Gastric Acid Reducing Agents		
Clinical Impact	• Co-administration of Acalabrutinib with a proton pump inhibitor, H2-r eceptor antagonist, or antacid may decrease Acalabrutinib plasma concentrations. • Decreased Acalabrutinib concentrations may reduce Acalabrutinib activity. • If treatment with a gastric acid reducing agent is required, consider using a H2-receptor antagonist (e.g., Ranitidine or Famotidine) or an Antacid (e.g., Calcium Carbonate).	
Prevention or Management	Antacids	Separate dosing by at least 2 hours.
	H2-receptor antagonists	Take Acalabrutinib 2 hours before taking the H2-receptor antagonist.
	Proton pump inhibitors	Avoid co-administration. Due to the long-lasting effect of proton pump inhibitors, separation of doses may not eliminate the interaction with Acalabrutinib.

Precautions:

Serious and Opportunistic Infections: Fatal and serious infections, including opportunistic infections, have occurred in patients with hematologic malignancies treated with Acalabrutinib. Serious or Grade 3 or higher infections (bacterial, viral, or fungal) occurred in 19% of 1029 patients exposed to Acalabrutinib in clinical trials, most often due to respiratory tract infections (11% of all patients, including pneumonia in 6%). These infections predominantly occurred in the absence of Grade 3 or 4 neutropenia, with neutropenic infection reported in 1.9% of all patients. Opportunistic infections in recipients of Acalabrutinib have included, but are not limited to, hepatitis B virus reactivation, fungal pneumonia, Pneumocystis jiroveci pneumonia, Epstein-Barr virus reactivation, cytomegalovirus, and progressive multifocal leukoencephalopathy (PML).

Hemorrhage: Fatal and serious hemorrhagic events have occurred in patients with hematologic malignancies treated with Acalabrutinib. Major hemorrhage (serious or Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 3.0% of patients, with fatal hemorrhage occurring in 0.1% of 1029 patients exposed to Acalabrutinib in clinical trials. Bleeding events of any grade, excluding bruising and petechiae, occurred in 22% of patients.

Cytopenias: Grade 3 or 4 cytopenias, including neutropenia (23%), anemia (8%), thrombocytopenia (7%), and lymphopenia (7%), developed in patients with hematologic malignancies treated with Acalabrutinib. Grade 4 neutropenia developed in 12% of patients. Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted.

Second Primary Malignancies: Second primary malignancies, including skin cancers and other solid tumors, occurred in 12% of 1029 patients exposed to Acalabrutinib in clinical trials. The most frequent second primary malignancy was skin cancer, reported in 6% of patients. Monitor patients for skin cancers and advise protection from sun exposure.

Atrial Fibrillation and Flutter: Grade 3 atrial fibrillation or flutter occurred in 1.1% of 1029 patients treated with Acalabrutinib, with all grades of atrial fibrillation or flutter reported in 4.1% of all patients. The risk may be increased in patients with cardiac risk factors, hypertension, previous arrhythmias, and acute infection. Monitor for symptoms of arrhythmia (e.g., palpitations, dizziness, syncope, dyspnea) and manage as appropriate.

Overdose: No information provided.

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

Packing: Each container contains 60 capsules in a box.