Acaluxen

Acalabrutinib 100 mg capsules

Everest

COMPOSITION

Acaluxen capsule: Each capsule contains Acalabrutinib INN 100 mg.

PHARMACOLOGY

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 survival.

Pharmacokinetics

The pharmacokinetics (PK) of Acalabrutinib was studied in healthy subjects and patients with B-cell malignancies. Acalabrutinib exhibits almost linear PK across a dose range of 75 to 250 mg (0.75 to 2.5 times the approved recommended single dose) and exhibits dose-proportionality. The daily area under the plasma drug concentration over time curve (AUC) was 1111 ng h/mL and maximum plasma concentration (Cmax) of Acalabrutinib was 323 ng/mL.

Absorption

The geometric mean absolute bioavailability of Acalabrutinib was 25%. Median time to peak Acalabrutinib plasma concentrations (Tmax) was 0.75 hours.

Effect of food

In healthy subjects, administration of a single 75 mg dose of Acalabrutinib (0.75 times the approved recommended single dose) with a high-fat, high-calorie meal (approximately 918 calories, 59 grams carbohydrate, 59 grams fat, and 39 grams protein) did not affect the mean AUC as compared to dosing under fasted conditions. Resulting Cmax decreased by 73% and Tmax was delayed 1-2 hours.

Distribution

The geometric mean (CV%) volume of distribution of Dacomitinib (Vss) was 1889 L (18%). In vitro binding of Dacomitinib to human plasma proteins is approximately 98% and is independent of drug concentrations from 250 ng/mL to 1000 ng/mL.

Elimination

Following a single oral dose of 100 mg Acalabrutinib, the median terminal elimination half-life (t1/2) of Acalabrutinib was 0.9 (range: 0.6 to 2.8) hours. The t1/2 of the active metabolite, ACP-5862, was 6.9 hours.

Acalabrutinib mean apparent oral clearance (CL/F) was 159 L/hr with similar PK between patients and healthy subjects, based on population PK analysis.

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 1% of the dose excreted as unchanged Acalabrutinib.

Specific Populations

Age, Race, and Body Weight

Age (42 to 90 years), sex, race (Caucasian, African American), and body weight did not have clinically meaningful effects on the PK of Acalabrutinib, based on population PK analysis.

Renal Impairment

Acalabrutinib undergoes minimal renal elimination. Based on population PK analysis, no clinically relevant PK difference was observed in 368 patients with mild or moderate renal impairment (eGFR ≥ 30 mL/min/1.73m2, as estimated by MDRD (modification of diet in renal disease equation)). Acalabrutinib PK has not been evaluated in patients with severe renal impairment (eGFR <29 mL/min/1.73m2, MDRD) or renal impairment requiring dialysis.

Hepatic Impairment

Acalabrutinib is metabolized in the liver. In a hepatic impairment study, compared to subjects with normal liver function (n=6), Acalabrutinib exposure (AUC) was increased by less than two-fold in subjects with mild (n=6) (Child-Pugh A) and moderate (n=6) (Child-Pugh B) hepatic impairment, respectively. Based on a population PK analysis, no clinically relevant PK difference was observed in subjects with mild (n=41) or moderate (n=3) hepatic impairment (total bilirubin between 1.5 to 3 times the upper limit of normal [ULN] and any AST) relative to subjects with normal (n=527) hepatic function (total bilirubin and AST within ULN). Acalabrutinib PK has not been evaluated in patients with severe hepatic impairment (Child-Pugh C or total bilirubin between 3 and 10 times ULN and any AST).

Drug Interaction Studies

Effect of CYP3A Inhibitors on Acalabrutinib

Co-administration with a strong CYP3A inhibitor (200 mg Itraconazole once daily for 5 days) increased the Acalabrutinib Cmax by 3.9-fold and AUC by 5.1-fold in healthy subjects. Physiologically based pharmacokinetic (PBPK) simulations with Acalabrutinib and moderate CYP3A inhibitors (erythromycin, fluconazole, diltiazem) showed that co-administration increased Acalabrutinib Cmax and AUC increased by 2- to almost 3-fold.

Effect of CYP3A Inducers on Acalabrutinib

Co-administration with a strong CYP3A inducer (600 mg rifampin once daily for 9 days) decreased Acalabrutinib Cmax by 68% and AUC by 77% in healthy subjects.

Gastric Acid Reducing Agents

Acalabrutinib solubility decreases with increasing pH. Co-administration with an antacid (1 g calcium carbonate) decreased Acalabrutinib AUC by 53% in healthy subjects. Co-administration with a proton pump inhibitor (40 mg omeprazole for 5 days) decreased Acalabrutinib AUC by 43%.

In Vitro Studies

Metabolic Pathways

Acalabrutinib is a weak inhibitor of CYP3A4/5, CYP2C8 and CYP2C9, but does not inhibit CYP1A2, CYP2B6, CYP2C19, and CYP2D6. The active metabolite (ACP-5862) is a weak inhibitor of CYP2C8, CYP2C9 and CYP2C19, but does not inhibit CYP1A2, CYP2B6, CYP2D6 and CYP3A4/5. Acalabrutinib is a weak inducer of CYP1A2, CYP2B6 and CYP3A4; the active metabolite (ACP-5862) weakly induces CYP3A4. Based on in vitro data and PBPK modeling, no interaction with CYP substrates is expected at clinically relevant concentrations.

Drug Transporter Systems

Acalabrutinib is a substrate of P-glycoprotein (P-gp) and BCRP. Acalabrutinib is not a substrate of renal uptake transporters OAT1, OAT3, and OCT2, or hepatic transporters OATP1B1, and OATP1B3. Acalabrutinib does not inhibit P-gp, OAT1, OAT3, OCT2, OATP1B1, and OATP1B3 at clinically relevant concentrations. Acalabrutinib may increase exposure to co-administered BCRP substrates (e.g., methotrexate) by inhibition of intestinal BCRP.

INDICATIONS AND USAGE

Acaluxen 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. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

DOSAGE AND ADMINISTRATION

Recommended Dosage

The recommended dose of Acaluxen is 100 mg taken orally approximately every twelve hours until disease progression or unacceptable toxicity.

Advise patients to swallow capsule whole with water. Advise patients not to open, break or chew the capsules. Acaluxen may be taken with or without food. If a dose of Acaluxen 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 Acaluxen should not be taken to make up for a missed dose.

Dose Modifications
Recommended Dose Modifications for Adverse Reactions: Dosage of Acalabrutinib can be reduced up to 100 mg daily for the toxicity has resolved to Grade 1 or baseline level. If the adverse reaction occurrence more than four times Acalabrutinib can be Discontinue.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Hemorrhage
Serious hemorrhagic events, including fatal events, have occurred in the combined safety database of 612 patients with hematologic malignancies treated with Acaluxen monotherapy. Grade 3 or higher bleeding events, including gastrointestinal, intracranial, and epistaxis have been reported in 2% of patients. Overall, bleeding events including bruising and petechiae of any grade occurred in approximately 50% of patients with hematological malignancies. The mechanism for the bleeding events is not well understood. Acaluxen may further 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 Acaluxen for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infection
Serious infections (bacterial, viral or fungal), including fatal events and opportunistic infections have occurred in the combined safety database of 612 patients with hematologic malignancies treated with Acalabrutinib monotherapy. Consider prophylaxis in patients who are at increased risk for opportunistic infections. Grade 3 or higher infections occurred in 18% of these patients. The most frequently reported Grade 3 or 4 infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation and progressive multifocal leukoencephalopathy (PML) have occurred. Monitor patients for signs and symptoms of infection and treat as medically appropriate.

Cytopenias
In the combined safety database of 612 patients with hematologic malignancies, patients treated with Acalabrutinib monotherapy experienced Grade 3 or 4 cytopenias, including neutropenia (23%), anemia (11%) and thrombocytopenia (8%) based on laboratory measurements. In the Acalabrutinib clinical Trial LY-004, patients' complete blood counts were assessed monthly during treatment.

Second Primary Malignancies
Second primary malignancies, including non-skin carcinomas, have occurred in 11% of patients with hematologic malignancies treated with Acaluxen monotherapy in the combined safety database of 612 patients. The most frequent second primary malignancy was skin cancer, reported in 7% of patients. Advise protection from sun exposure.

Atrial Fibrillation and Flutter
In the combined safety database of 612 patients with hematologic malignancies treated with Acalabrutinib monotherapy, atrial fibrillation and atrial flutter of any grade occurred in 3% of patients, and Grade 3 in 1% of patients. Monitor for atrial fibrillation and atrial flutter and manage as appropriate.

SIDE EFFECTS
The following adverse reactions are discussed in greater detail in other sections of the labeling:
- Hemorrhage
- Infection
- Second Primary Malignancies
- Cytopenias

DRUG INTERACTIONS
Strong CYP3A Inhibitors
Co-administration of Acaluxen with a strong CYP3A inhibitor (itraconazole) increased Acalabrutinib plasma concentrations & increased Acalabrutinib concentrations may result in increased toxicity.

Moderate CYP3A Inhibitors
Co-administration of Acaluxen with a moderate CYP3A inhibitor may increase Acalabrutinib plasma concentrations & increased Acalabrutinib concentrations may result in increased toxicity.

Strong CYP3A Inducers
Co-administration of Acaluxen with a strong CYP3A inducer (rifampin) decreased Acalabrutinib plasma concentrations & decreased Acalabrutinib concentrations may reduce Acaluxen activity.

Gastric Acid Reducing Agents
Co-administration of Acaluxen with a proton pump inhibitor, H2-receptor antagonist, or antacid may decrease Acalabrutinib plasma concentrations. Decreased Acalabrutinib concentrations may reduce Acaluxen 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).

USE IN SPECIFIC POPULATIONS
Pregnancy
Based on findings in animals, Acalabrutinib may cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of Acalabrutinib to pregnant rabbits during organogenesis resulted in reduced fetal growth at maternal exposures (AUC) approximately 4 times exposures in patients at the recommended dose of 100 mg twice daily. Advise pregnant women of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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, advise lactating women not to breastfeed while taking Acalabrutinib and for at least 2 weeks after the final dose.

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

Geriatric Use
Eighty (64.5%) of the 124 MCL patients in clinical trials of Acaluxen were 65 years of age or older, and 32 patients (25.8%) were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients ≥ 65 years and younger.

PHARMACEUTICAL INFORMATION
Storage Condition
Store below 30°C, in a cool and dry place. Keep away from light. Keep out of the reach of children.

How Supplied
Acaluxen capsule: Each HDPE container contains 60 capsules (each capsule contains 100 mg Acalabrutinib) a silica gel desiccant and polyester coil with a child-resistant closure.

Manufactured by
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