Alpesib

Alpelisib 150 mg tablets

Everest

COMPOSITION

ALPESIB tablet: Each film coated tablet contains Alpelisib INN 150 mg.

PHARMACOLOGY

Mechanism of Action

Alpelisib is an inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominantly against PI3Kα. Gain-of-function mutations in the gene encoding the catalytic α-subunit of PI3K (PIK3CA) lead to activation of PI3Kα and Akt-signaling, cellular transformation and the generation of tumors in in vitro and in vivo models.

In breast cancer cell lines, Alpelisib inhibited the phosphorylation of PI3K downstream targets, including Akt and showed activity in cell lines harboring a PIK3CA mutation. In vivo, Alpelisib inhibited the PI3K/Akt signaling pathway and reduced tumor growth in xenograft models, including models of breast cancer.

PI3K inhibition by Alpelisib treatment has been shown to induce an increase in estrogen receptor (ER) transcription in breast cancer cells. The combination of Alpelisib and fulvestrant demonstrated increased antitumor activity compared to either treatment alone in xenograft models derived from ER-positive, PIK3CA mutated breast cancer cell lines.

Pharmacokinetic properties

The pharmacokinetics of Alpelisib has been studied in healthy subjects and adult patients with solid tumors. Steady-state Alpelisib maximum plasma concentration (C_{max}) and AUC increased proportionally over the dose range of 30 mg to 450 mg (0.1 to 1.5 times the approved recommended dosage) under fed conditions. The mean accumulation of Alpelisib is 1.3 to 1.5 and steady-state plasma concentrations are reached within 3 days following daily dosage. In adult patients who received Alpelisib 300 mg once daily in the SOLAR-1 trial, population approach derived mean steady-state Alpelisib [coefficient of variation (CV%)] for C_{max} was 2480 (23%) ng/mL and $AUC_{0\text{-}24hr}$ was 33224 (21%) ng*h/mL.

Absorption

The median time to reach peak plasma concentration (T_{max}) ranged between 2.0 to 4.0 hours.

Effect of food

A high-fat high-calorie meal (985 calories with 58.1 g of fat) increased Alpelisib AUC by 73% and C_{max} by 84%, and a low-fat low-calorie meal (334 calories with 8.7 g of fat) increased Alpelisib AUC by 77% and C_{max} by 145% following a single dose of Alpelisib. No clinically significant differences in Alpelisib AUC were observed between low-fat low-calorie and high-fat high-calorie meals.

Distribution

The mean (% CV) apparent volume of distribution of Alpelisib at steady-state is predicted to be 114 L (46%). Protein binding of Alpelisib is 89% and is independent of concentration.

Elimination

The half-life of Alpelisib is predicted to be 8 to 9 hours. The mean (% CV) clearance of Alpelisib is predicted to be 9.2 L/hr (21%) under fed conditions.

Metabolism

Alpelisib is primarily metabolized by chemical and enzymatic hydrolysis to form its metabolite BZG791 and to a lesser extent by CYP3A4, in vitro.

Excretion

Following a single oral dose of 400 mg radiolabeled Alpelisib under fasted condition, 81% of the administered dose was recovered in feces (36% unchanged, 32% BZG791) and 14% (2% unchanged, 7.1% BZG791) in urine. CYP3A4-mediated metabolites (12%) and glucuronides amounted to approximately 15% of the dose.

Specific Populations

No clinically significant differences in the pharmacokinetics of Alpelisib were predicted based on age (21 to 87 years), sex, race/ethnicity (Japanese or Caucasian), body weight (37 to 181 kg), mild to moderate renal impairment (CLcr 30 to < 90 mL/min based on the Cockcroft-Gault formula), or mild to severe hepatic impairment (Child-Pugh Class A, B, and C). The effect of severe renal impairment (CLcr < 30 mL/min) on the pharmacokinetics of Alpelisib is unknown.

Drug Interaction Studies

Clinical Studies

Acid Reducing Agents: Alpelisib can be coadministered with acid reducing agents, since Alpelisib should be taken with food. Food exhibited a more pronounced effect on the solubility of Alpelisib than the effect of gastric pH value.

Coadministration of the H2 receptor antagonist ranitidine in combination with a single 300 mg oral dose of Alpelisib decreased the absorption and overall exposure of Alpelisib. In the presence of a low-fat low-calorie meal, AUC was decreased on average by 21% and Cmax by 36% with ranitidine. Under the fasted state, AUC was decreased on average by 30% and Cmax by 51% with ranitidine.

CYP3A4 Substrates: No clinically significant differences in pharmacokinetics of everolimus (a substrate of CYP3A4 and P-gp) were observed when coadministered with Alpelisib.

In Vitro Studies

Effect of Alpelisib on CYP Enzymes: Alpelisib inhibits CYP3A4 in a time-dependent manner and induces CYP2B6, CYP2C9 and CYP3A4.

Effect of Transporter on Alpelisib: Alpelisib is a substrate of BCRP.

Effect of Alpelisib on Transporters: Alpelisib is an inhibitor of P-gp. Alpelisib has a low potential to inhibit BCRP, MRP2, BSEP, OATP1B1, OATP1B3, OCT1, OAT1, OAT3, OCT2, MATE1, and MATE2K at clinically relevant concentrations.

INDICATIONS AND USAGE

Alpelisib is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CAmutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

DOSAGE AND ADMINISTRATION

The recommended dose of Alpelisib is 300 mg (two 150 mg film coated tablets) taken orally, once daily, with food.

Continue treatment until disease progression or unacceptable toxicity occurs.

Patients should take their dose of Alpelisib at approximately the same time each day.

Swallow Alpelisib tablets whole (tablets should not be chewed, crushed or split prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.

If a dose of Alpelisib is missed, it can be taken with food within 9 hours after the time it is usually taken. After more than 9 hours, skip the dose for that day. The next day, take Alpelisib at the usual time.

If the patient vomits after taking the dose, advise the patient not to take an additional dose on that day, and to resume the dosing schedule the next day at the usual time.

When given with Alpelisib, the recommended dose of fulvestrant is 500 mg administered on Days 1, 15, and 29, and once monthly thereafter. Refer to the Full Prescribing Information for fulvestrant.

CONTRAINDICATIONS

Alpelisib is contraindicated in patients with severe hypersensitivity to it or any of its components.

WARNINGS AND PRECAUTIONS

Severe Hypersensitivity

Advise patients of the signs and symptoms of severe hypersensitivity reactions. Permanently discontinue Alpelisib in the event of severe hypersensitivity.

Severe Cutaneous Reactions

Severe cutaneous reactions, including Stevens-Johnson Syndrome (SJS) and Erythema Multiforme (EM) were reported in patients treated with Alpelisib.

Advise patients of the signs and symptoms of severe cutaneous reactions (e.g., a prodrome of fever, flu-like symptoms, mucosal lesions or progressive skin rash).

Hyperglycemia

Before initiating treatment with Alpelisib, test FPG, HbA1c, and optimize blood glucose. After initiating treatment with Alpelisib, monitor blood glucose and/or FPG at least once every week for the first 2 weeks, then at least once every 4 weeks, and as clinically indicated. Monitor HbA1c every 3 months and as clinically indicated.

Based on the severity of the hyperglycemia, Alpelisib may require dose interruption, reduction, or discontinuation.

Pneumonitis

Permanently discontinue Alpelisib in all patients with confirmed pneumonitis.

Advise patients to immediately report new or worsening respiratory symptoms.

Diarrhea

Advise patients to start antidiarrheal treatment, increase oral fluids, and notify their healthcare provider if diarrhea occurs while taking Alpelisib.

Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, Alpelisib can cause fetal harm when administered to a pregnant woman.

SIDE EFFECTS

- Severe allergic reactions
- Diarrhea
- Severe skin reactions
- Lung problems (pneumonitis)
- High blood sugar levels (hyperglycemia)

DRUG INTERACTIONS

Effect of Other Drugs on Alpelisib

CYP3A4 Inducer

Coadministration of Alpelisib with a strong CYP3A4 inducer may decrease alpelisib concentration, which may decrease Alpelisib activity. Avoid coadministration of Alpelisib with strong CYP3A4 inducers.

BCRP Inhibitors

Coadministration of Alpelisib with a BCRP inhibitor may increase Alpelisib concentration, which may increase the risk of toxicities. Avoid the use of BCRP inhibitors in patients treated with Alpelisib. If unable to use alternative drugs, when Alpelisib is used in combination with BCRP inhibitors, closely monitor for increased adverse reactions.

Effect of Alpelisib on Other Drugs

CYP2C9 Substrates

Coadministration of Alpelisib with CYP2C9 substrates (e.g., Warfarin) may reduce plasma concentration of these drugs. Closely monitor when Alpelisib is used in combination with CYP2C9 substrates where decreases in the plasma concentration of CYP2C9 substrates may reduce activity of these drugs.

USE IN SPECIFIC POPULATIONS

Pregnancy

Based on animal data and mechanism of action, Alpelisib can cause fetal harm when administered to a pregnant woman.

Lactation

There is no data on the presence of Alpelisib in human milk, its effects on milk production, or the breastfed child. Because of the potential for serious adverse reactions in the breastfed child, advise lactating women to not breastfeed during treatment with Alpelisib and for 1 week after the last dose.

Females and Males of Reproductive Potential

Infertility

Based on findings from animal studies, Alpelisib may impair fertility in males and females of reproductive potential.

Pediatric Use

The safety and efficacy of Alpelisib in pediatric patients have not been established

Geriatric Use

No overall differences in effectiveness of Alpelisib were observed between patients ≥ 65 years of age compared to younger patients. There are an insufficient number of patients ≥ 75 years of age to assess whether there are differences in safety or effectiveness.

Renal Impairment

The effect of severe renal impairment (CLcr < 30 mL/min) on Alpelisib pharmacokinetics is unknown.

No dose adjustment is recommended for patients with mild to moderate renal impairment (CLcr 30 to < 90 mL/min).

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

ALPESIB tablet: Each HDPE container contains 28 tablets (each tablet contains 150 mg Alpelisib) a silica gel desiccant and polyester coil with a child-resistant closure.

Manufactured by
Everest Pharmaceuticals Ltd.
BSCIC I/A, Kanchpur, Narayanganj, Bangladesh
www.everestpharmabd.com
1901000126