Capivast

Capivasertib INN

Everest

COMPOSITION

CAPIVAST tablet: Each film coated tablet contains Capivasertib INN 200 mg.

PHARMACOLOGY

Capivasertib is an inhibitor of all 3 isoforms of serine/threonine kinase AKT (AKT1, AKT2 and AKT3) and inhibits phosphorylation of downstream AKT substrates. AKT activation in tumors is a result of activation of upstream signaling pathways, mutations in AKT1, loss of phosphatase and tensin homolog (PTEN) function and mutations in the catalytic subunit alpha of phosphatidylinositol 3-kinase (PIK3CA). In vitro, capivasertib reduced growth of breast cancer cell lines including those with relevant PIK3CA or AKT1 mutations or PTEN alteration. In vivo, capivasertib alone and in combination with Fulvestrant inhibited tumor growth of mouse xenograft models including estrogen receptor positive breast cancer models with alterations in PIK3CA, AKT1, and PTEN.

INDICATIONS AND USAGE

Capivasertib is a kinase inhibitor indicated, in combination with Fulvestrant for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.

DOSAGE AND ADMINISTRATION

Patients Selection: Presence of one or more of the following genetic alterations in tumor tissue: PIK3CA/AKT1/PTEN.

Recommended Evaluation Before Initiating Capivasertib:

Evaluate fasting blood glucose (FG) and hemoglobin A1C (HbA1C) prior to starting Capivasertib and at regular intervals during treatment.

Recommended Dosage:

The recommended dosage of Capivasertib, in combination with Fulvestrant, is 400 mg orally twice daily (approximately 12 hours apart) with or without food, for 4 days followed by 3 days off. Continue Capivasertib until disease progression or unacceptable toxicity.

Capivasertib dosing schedule for each week is provided in Table 1.

Day	1	2	3	4	5*	6*	7*
Morning	2x200 mg	2x200 mg	2x200 mg	2x200 mg			
Evening	2x200 mg	2x200 mg	2x200 mg	2x200 mg			

* No dosing on day 5, 6 and 7.

Swallow Capivasertib tablets whole. Do not chew, crush, or split tablets prior to swallowing. Do not take tablets that are broken, cracked, or otherwise not intact. If a patient misses a dose within 4 hours of the scheduled time, instruct the patient to take the missed dose. If a patient misses a dose more than 4 hours of the scheduled time, instruct the patient to skip the dose and take the next dose at its usual scheduled time. If a patient vomits a dose, instruct the patient not to take an additional dose and take the next dose at its usual scheduled time.

For premenopausal and perimenopausal women, administer a luteinizing hormonereleasing hormone (LHRH) agonist according to current clinical practice standards. For men, consider administering a LHRH agonist according to current clinical practice standards.

Dosage Modifications for Adverse Reactions

The recommended dose reductions for adverse reactions are listed in Table 2. Permanently discontinue Capivasertib if unable to tolerate the second dose reduction.

Table 2: Recommended Dose Reductions of Capivasertib for Adverse Reactions

Capivasertib	Dose and Schedule
First dose reduction	320 mg twice daily for 4 days followed by 3 days off
Second dose reduction	200 mg twice daily for 4 days followed by 3 days off

The recommended dosage modifications for adverse reactions are provided in Table 3.

Table 3: Recommended Dosage Modifications of Capivasertib for Adverse Reactions

Adverse Reaction	Severity*	Capivasertib Dosage Modification
Hyperglycemia (Fasting Glucose [FG])	FG > ULN-160 mg/dL or FG > ULN-8.9 mmol/L or HbA1C > 7%	Consider initiation or intensification of oral anti-diabetic treatment.
	FG 161-250 mg/dL or FG 9-13.9 mmol/L	Withhold Capivasertib until FG decrease ≤ 160 mg/dL (or ≤ 8.9 mmol/L). If recovery occurs in ≤ 28 days, resume Capivasertib at same dose. If recovery occurs in > 28 days, resume Capivasertib at one lower dose.
	FG 251-500 mg/dL or FG 14-27.8 mmol/L	Withhold Capivasertib until FG decrease ≤ 160 mg/dL (or ≤ 8.9 mmol/L). If recovery occurs in ≤ 28 days, resume Capivasertib at one lower dose. If recovery occurs in > 28 days, permanently discontinue Capivasertib.
	FG> 500 mg/dL or FG > 27.8 mmol/L or life-threatening sequelae of hyperglycemia at any FG level	For life-threatening sequelae of hyperglycemia or if FG persists at ≥ 500 mg/dL after 24 hours, permanently discontinue Capivasertib. If FG ≤ 500 mg/dL (or ≤ 27.8 mmol/L) within 24 hours, then follow the guidance in the table for the relevant grade.
Diarrhea	Grade 2	Withhold Capivasertib until recovery to ≤ Grade 1. If recovery occurs in ≤ 28 days, resume Capivasertib at same dose or one lower dose as clinically indicated. If recovery occurs in > 28 days, resume at one lower dose as clinically indicated. For recurrence, reduce Capivasertib by one lower dose.
	Grade 3	Withhold Capivasertib until recovery to ≤ Grade 1. If recovery occurs in ≤ 28 days, resume Capivasertib at same dose or one lower dose as clinically indicated. If recovery occurs in > 28 days, permanently discontinue Capivasertib.
	Grade 4	Permanently discontinue Capivasertib.
Cutaneous Adverse Reactions	Grade 2	Withhold Capivasertib until recovery to ≤ Grade 1. Resume Capivasertib at the same dose. Persistent or recurrent: reduce Capivasertib by one lower dose.
	Grade 3	Withhold Capivasertib until recovery to ≤ Grade 1. If recovery occurs in ≤ 28 days, resume Capivasertib at same dose.

Adverse Reaction	Severity*	Capivasertib Dosage Modification
Cutaneous Adverse Reactions	Grade 3 (cont'd)	If recovery occurs in > 28 days, resume Capivasertib at one lower dose. For recurrent Grade 3, permanently discontinue Capivasertib.
	Grade 4	Permanently discontinue Capivasertib.
Other Adverse Reactions	Grade 2	Withhold Capivasertib until recovery to ≤ Grade 1. Resume Capivasertib at the same dose.
	Grade 3	Withhold Capivasertib until recovery to ≤ Grade 1. If recovery occurs in ≤ 28 days, resume Capivasertib at same dose. If recovery occurs in > 28 days, resume Capivasertib at one lower dose.
	Grade 4	Permanently discontinue Capivasertib.

*Severity grading according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Dosage Modifications for Strong and Moderate CYP3A Inhibitors
Avoid concomitant use with strong CYP3A inhibitors. If concomitant use with a strong CYP3A inhibitor cannot be avoided, reduce the dosage of Capivasertib to 320 mg orally twice daily for 4 days followed by 3 days off.

When concomitantly used with a moderate CYP3A inhibitor, reduce the dosage of Capivasertib to 320 mg orally twice daily for 4 days followed by 3 days off.

After discontinuation of a strong or moderate CYP3A inhibitor, resume the Capivasertib dosage (after 3 to 5 half-lives of the inhibitor) that was taken prior to initiating the strong or moderate CYP3A inhibitor.

CONTRAINDICATIONS
Severe hypersensitivity to Capivasertib or any of its components.

WARNINGS AND PRECAUTION
Hyperglycemia
Evaluate blood glucose levels prior to starting and at regular intervals during treatment. Withhold, reduce dose, or permanently discontinue Capivasertib based on severity.

Diarrhea
Capivasertib caused diarrhea in most patients. Advise patients to increase oral fluids, start antidiarrheal treatment, and consult with a healthcare provider if diarrhea occurs while taking Capivasertib. Withhold, reduce dose, or permanently discontinue Capivasertib based on severity.

Cutaneous Adverse Reactions
Monitor for signs and symptoms of cutaneous adverse reactions. Withhold, reduce dose, or permanently discontinue Capivasertib based on severity.

Embryo-Fetal Toxicity
Capivasertib can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception.

ADVERSE REACTIONS
Most common adverse reactions (incidence ≥20%), including laboratory abnormalities, were diarrhea, cutaneous adverse reactions, increased random glucose, decreased lymphocytes, decreased hemoglobin, increased fasting glucose, nausea, fatigue, decreased leukocytes, increased triglycerides, decreased neutrophils, increased creatinine, vomiting and stomatitis.

USE IN SPECIFIC POPULATIONS
Pregnancy
Capivasertib is used in combination with fulvestrant, poses potential risks to fetal development based on animal studies and its mechanism of action, although no human data is available. In rat studies, capivasertib caused adverse effects including embryo-fetal mortality and reduced fetal weights at exposures lower than the recommended human dose. These effects occurred alongside maternal toxicity. Given these findings, pregnant women and those of reproductive potential should be advised of the potential fetal risks.

Lactation
Advise not to breastfeed.

Females and Males of Reproductive Potential
Capivasertib can cause fetal harm when administered to pregnant women.

Pregnancy Testing
Pregnancy status of females of reproductive potential should verify prior to initiating Capivasertib.

Contraception
Females
Females of reproductive potential are adviced to use effective contraception during treatment with Capivasertib and for 1 month after the last dose.

Males
Male patients with female partners of reproductive potential are adviced to use effective contraception during treatment with Capivasertib and for 4 months after the last dose.

Pediatric Use
No data available for pediatric patients.

Hepatic Impairment
No dosage modification is recommended for patients with mild hepatic impairment (bilirubin ≤ upper limit of normal (ULN) and AST > ULN or bilirubin > 1 to 1.5x ULN and any AST). Monitor patients with moderate (bilirubin > 1.5 to 3x ULN and any AST) hepatic impairment for adverse reactions due to potential increased capivasertib exposure. Capivasertib has not been studied in patients with severe (bilirubin > 3x ULN and any AST) hepatic impairment.

OVERDOSE
In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

DRUG INTERACTIONS
Strong CYP3A Inhibitors
Avoid concomitant use. If concomitant use cannot be avoided, reduce Capivasertib dose.

Moderate CYP3A Inhibitors
Reduce Capivasertib dose.

Strong and Moderate CYP3A Inducers
Avoid concomitant use.

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
CAPIVAST tablet: Each HDPE container contains 64 tablets, a silica gel desiccant and polyester coil with child resistant closure.

Manufactured by
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