Cabozanix
Cabozantinib

COMPOSITIONS

Cabozanix 20 Capsule: Each hard gelatin capsule contains Cabozantinib (S)-Malate equivalent to 20 mg Cabozantinib.

Cabozanix 80 Capsule: Each hard gelatin capsule contains Cabozantinib (S)-Malate equivalent to 80 mg Cabozantinib.

THERAPEUTIC CLASS: Anti-cancer

CLINICAL PHARMACOLOGY

Mechanism of Action:

In vitro biochemical and/or cellular assays have shown that Cabozantinib inhibits the tyrosine kinase activity of RET, MET, VEGFR-1, -2 and -3, KIT, TRKB, FLT-3, AXL, ROS1, TYRO3, MER, and TIE-2. These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, drug resistance, and maintenance of the tumor microenvironment.

Pharmacodynamics

Cardiac Electrophysiology

The effect of orally administered Cabozantinib 140 mg on QTc interval was evaluated in a randomized, double-blinded, placebo-controlled study in patients with MTC. A mean increase in QTcF of 10 - 15 ms was observed at 4 weeks after initiating Cabozantinib. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No Cabozantinib -treated patients had a QTcF > 500 ms

Pharmacokinetics

A population pharmacokinetic analysis of Cabozantinib was performed using data collected from 289 patients with solid tumors including MTC following oral administration of 140 mg daily doses. Repeat daily dosing of Cabozantinib at 140 mg for 19 days resulted in 4-to 5-fold mean Cabozantinib accumulation (based on AUC) compared to a single dose administration; steady state was achieved by Day 15.

Absorption

Following oral administration of Cabozantinib, median time to peak Cabozantinib plasma concentrations (T_{max}) ranged from 2 to 5 hours post-dose.

A 19% increase in the C_{max} of the tablet formulation Cabozantinib compared to the capsule formulation was observed following a single 140 mg dose. A less than 10% difference in the AUC was observed between Cabozantinib tablet and Cabozantinib capsule formulations.

Cabozantinib C_{max} and AUC values increased by 41% and 57%, respectively, following a high fat meal relative to fasted conditions in healthy subjects administered a single 140 mg oral Cabozantinib dose.

Distribution

The oral volume of distribution (V/F) of Cabozantinib is approximately 349 L. Cabozantinib is highly protein bound in human plasma (≥99.7%).

Elimination

The predicted effective half-life is approximately 55 hours and the clearance (CL/F) at steady-state is estimated to be 4.4 L/hr.

Metabolism

Cabozantinib is a substrate of CYP3A4 *in vitro*.

Excretion

Approximately 81% of the total administered radioactivity was recovered within a 48-day collection period following a single 140 mg dose of an investigational ^{14}C-Cabozantinib formulation in healthy subjects. Approximately 54% was recovered in feces and 27% in urine. Unchanged Cabozantinib accounted for 43% of the total radioactivity in feces and was not detectable in urine following a 72 hour collection.

INDICATIONS

Cabozantinib is indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC).

DOSAGE AND ADMINISTRATION

Recommended Dose

Do NOT substitute Cabozantinib capsules with Cabozantinib tablets. The recommended daily dose of Cabozantinib is 140 mg (one 80-mg and three 20-mg capsules). Do not administer Cabozantinib with food. Instruct patients not to eat for at least 2 hours before and at least 1 hour after taking Cabozantinib. Continue treatment until disease progression or unacceptable toxicity occurs.

Swallow Cabozantinib capsules whole. Do not open Cabozantinib capsules.

Do not take a missed dose within 12 hours of the next dose.

Do not ingest foods (e.g., grapefruit, grapefruit juice) or nutritional supplements that are known to inhibit cytochrome P450 while taking Cabozantinib.

In Patients with Hepatic Impairment: The recommended starting dose of Cabozantinib for patients with mild to moderate hepatic impairment is 80 mg.

Dosage Modifications:

For Adverse Reactions

Withhold Cabozantinib for NCI CTCAE Grade 4 hematologic adverse reactions, Grade 3 or greater non-hematologic adverse reactions or intolerable Grade 2 adverse reactions. Upon resolution/improvement of the adverse reaction (i.e., return to baseline or resolution to Grade 1), reduce the dose as follows:

- If previously receiving 140 mg daily dose, resume treatment at 100 mg daily (one 80-mg and one 20- mg capsule)
- If previously receiving 100 mg daily dose, resume treatment at 60 mg daily (three 20-mg capsules)
- If previously receiving 60 mg daily dose, resume at 60 mg if tolerated, otherwise, discontinue Cabozantinib.

Permanently discontinue Cabozantinib for any of the following:

- Development of visceral perforation or fistula formation
- Severe hemorrhage
- Serious arterial thromboembolic event (e.g., myocardial infarction, cerebral infarction)
- Nephrotic syndrome
- Malignant hypertension, hypertensive crisis, persistent uncontrolled hypertension despite optimal medical management
- Osteonecrosis of the jaw
- Reversible posterior leukoencephalopathy syndrome.

In Patients Concurrently Taking a Strong CYP3A4 Inhibitor

Reduce the daily Cabozantinib dose by 40 mg (for example, from 140 mg to 100 mg daily or from 100 mg to 60 mg daily). Resume the dose that was used prior to initiating the CYP3A4 inhibitor 2 to 3 days after discontinuation of the strong inhibitor.

In Patients Concurrently Taking a Strong CYP3A4 Inducer

Increase the daily Cabozantinib dose by 40 mg (for example, from 140 mg to 180 mg daily or from 100 mg to 140 mg daily) as tolerated. Resume the dose that was used prior to initiating the CYP3A4 inducer 2 to 3 days after discontinuation of the strong inducer. The daily dose of Cabozantinib should not exceed 180 mg

USE IN SPECIFIC POPULATIONS

Pregnancy

Based on findings from animal studies and its mechanism of action, Cabozantinib can 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 developmental and reproductive toxicology studies administration of Cabozantinib to pregnant rats and rabbits during organogenesis resulted in embryofetal lethality and structural anomalies at exposures that were below those occurring clinically at the recommended dose. Advise pregnant women or women of childbearing potential of the potential hazard to a 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 Cabozantinib or its metabolites in human milk, or their effects on the breastfed infant, or milk production. Because of the potential for serious adverse reactions in a breastfed infant from Cabozantinib, advise a lactating woman not to breastfeed during treatment with Cabozantinib and for 4 months after the final dose.

Females and Males of Reproductive Potential

Contraception

Females

Cabozantinib can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with Cabozantinib and for 4 months after the final dose.

Infertility

Females and Males

Based on findings in animals, Cabozantinib may impair fertility in females and males of reproductive potential.

Pediatric Use

The safety and effectiveness of Cabozantinib in pediatric patients have not been studied.

Geriatric Use

Clinical studies of Cabozantinib did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients.

Hepatic Impairment

Increased exposure to Cabozantinib has been observed in patients with mild to moderate hepatic impairment. Reduce the starting dose of Cabozantinib in patients with mild (Child-Pugh score (C-P) A) or moderate (C-P B) hepatic impairment. Cabozantinib is not recommended for use in patients with severe hepatic impairment.

Renal Impairment

Dosage adjustment is not required in patients with mild or moderate renal impairment. There is no experience with Cabozantinib in patients with severe renal impairment.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- Thrombotic Events: Discontinue Cabozantinib for myocardial infarction, cerebral infarction, or other serious arterial thromboembolic events.
- Wound Complications: Withhold Cabozantinib for dehiscence or complications requiring medical intervention.
- Hypertension: Monitor blood pressure regularly. Discontinue Cabozantinib for hypertensive crisis.
- Osteonecrosis of the jaw: Discontinue Cabozantinib.
- Palmar-plantar Erythrodysesthesia Syndrome (PPES): Interrupt Cabozantinib, decrease dose.
- Proteinuria: Monitor urine protein. Discontinue for nephrotic syndrome.
- Reversible posterior leukoencephalopathy syndrome (RPLS): Discontinue Cabozantinib.
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.

ADVERSE REACTIONS

The most commonly reported adverse drug reactions (≥25%) are diarrhea, stomatitis, Palmar-plantar Erythrodysesthesia Syndrome (PPES), decreased weight, decreased appetite, nausea, fatigue, oral pain, hair color changes, dysgeusia, hypertension, abdominal pain, and constipation. The most common laboratory abnormalities (≥25%) are increased AST, increased ALT, lymphopenia, increased alkaline phosphatase, hypocalcemia, neutropenia, thrombocytopenia, hypophosphatemia, and hyperbilirubinemia.

DRUG INTERACTIONS

Effect of CYP3A4 Inhibitors

Administration of a strong CYP3A4 inhibitor, Ketoconazole to healthy subjects increased single dose plasma Cabozantinib exposure by 38%. Avoid taking a strong CYP3A4 inhibitor (e.g., Ketoconazole, Itraconazole, Clarithromycin, Atazanavir, Indinavir, Nefazodone, Nelfinavir, Ritonavir, Saquinavir, Telithromycin, Voriconazole) while taking Cabozantinib or reduce the dosage of Cabozantinib if concomitant use with strong CYP3A4 inhibitors cannot be avoided.

Avoid ingestion of foods (e.g., grapefruit, grapefruit juice) or nutritional supplements that are known to inhibit cytochrome P450 while taking Cabozantinib.

Effect of CYP3A4 Inducers

Administration of a strong CYP3A4 inducer, Rifampin to healthy subjects decreased single-dose plasma Cabozantinib exposure by 77%. Avoid chronic co-administration of strong CYP3A4 inducers (e.g., Phenytoin, Carbamazepine, Rifampin, Rifabutin, Rifapentine, Phenobarbital, St. John's Wort) with Cabozantinib or increase the dosage of Cabozantinib if concomitant use with strong CYP3A4 inducers cannot be avoided.

Effect of MRP2 Inhibitors

Concomitant administration of MRP2 inhibitors may increase the exposure to Cabozantinib. Monitor patients for increased toxicity when MRP2 inhibitors (e.g., Abacavir, Adefovir, Cidofovir, Furosemide, Lamivudine, Nevirapine, Ritonavir, Probenecid, Saquinavir, and Tenofovir) are co-administered with Cabozantinib.

PHARMACEUTICAL INFORMATION

Storage conditions

Store at below 30^{0}C and dry place, away from light. Keep out of the reach of children.

Presentation & Packaging

Cabozanix 20 Capsule: Each commercial box contains 90 Capsules in HDPE pot.

Cabozanix 80 Capsule: Each commercial box contains 30 Capsules in HDPE pot.

Only for Export

Manufactured By
Beacon Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

Marketed By
BEACON®
Medicare Limited
Dhaka, Bangladesh

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