Caboxen

Cabozantinib 20 mg & 80 mg capsules

Everest

COMPOSITION

CABOXEN 20 capsule: Each capsule contains Cabozantinib (S)-malate INN equivalent to 20 mg Cabozantinib.

CABOXEN 80 capsule: Each capsule contains Cabozantinib (S)-malate INN equivalent to 80 mg Cabozantinib.

CLINICAL PHARMACOLOGY

Mechanism of Action

In vitro biochemical and/or cellular assays have shown that Cabozantinib inhibits the tyrosine kinase activity of MET, VEGFR-1, -2 and -3, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, 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.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of Cabozantinib has been evaluated in two species: rasH2 transgenic mice and Sprague-Dawley rats. In the 2-year rat carcinogenicity study, once daily oral administration of Cabozantinib resulted in a statistically significant increase in the incidence of malignant/complex malignant pheochromocytoma in combination with benign pheochromocytoma or in benign pheochromocytoma alone in male rats at a dose of 1 mg/kg (approximately 5 times the human exposure by AUC at the recommended 60 mg dose). Cabozantinib was not carcinogenic in a 26-week carcinogenicity study in rasH2 transgenic mice at a slightly higher exposure than the intended human therapeutic exposure.

Cabozantinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay and was not clastogenic in both the *in vitro* cytogenetic assay using human lymphocytes or in the *in vivo* mouse micronucleus assay.

Based on nonclinical findings, male and female fertility may be impaired by treatment with Cabozantinib. In a fertility study in which Cabozantinib was administered to male and female rats at doses of 1, 2.5, and 5 mg/kg/day, male fertility was significantly compromised at doses equal to or greater than 2.5 mg/kg/day (approximately 13-fold of human AUC at the recommended dose), with a decrease in sperm counts and reproductive organ weights. In females, fertility was significantly reduced at doses equal to or greater than 1 mg/kg/day (5-fold of human AUC at the recommended dose) with a significant decrease in the number of live embryos and a significant increase in pre- and post-implantation losses.

Observations of effects on reproductive tract tissues in general toxicology studies were supportive of effects noted in the dedicated fertility study and included hypospermia and absence of corpora lutea in male and female dogs in a 6-month repeat dose study at plasma exposures (AUC) approximately 0.5-fold (males) and <0.1-fold (females) of those expected in humans at the recommended dose. In addition, female rats administered 5 mg/kg/day for 14 days (approximately 9-fold of human AUC at the recommended dose) exhibited ovarian necrosis.

INDICATIONS AND USAGE

Thyroid Cancer

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

DOSAGE AND ADMINISTRATION

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.

Do NOT substitute Cabozantinib capsules with Cabozantinib tablets.

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.

CONTRAINDICATION

None

WARNINGS AND PRECAUTIONS

Perforations and Fistulas

Gastrointestinal (GI) perforations and fistulas were reported in 3% and 1% of Cabozantinib treated patients, respectively. All were serious and one GI fistula was fatal (< 1%). Non-GI fistulas including tracheal/esophageal were reported in 4% of Cabozantinib -treated patients. Two (1%) of these were fatal.

Monitor patients for symptoms of perforations and fistulas, (including abscess). Discontinue cabozantinib patients who experience a perforation or a fistula.

Hemorrhage

Serious and sometimes fatal hemorrhage occurred with Cabozantinib. The incidence of Grade ≥ 3 hemorrhagic events was higher in Cabozantinib -treated patients compared with placebo (3% vs. 1%).

Do not administer Cabozantinib to patients with a recent history of hemorrhage or hemoptysis.

Thrombotic Events

Cabozantinib treatment results in an increased incidence of thrombotic events (venous thromboembolism: 6% vs. 3% and arterial thromboembolism: 2% vs. 0% in Cabozantinib-treated and placebo-treated patients, respectively).

Discontinue Cabozantinib in patients who develop an acute myocardial infarction or any other clinically significant arterial thromboembolic complication.

Wound Complications

Wound complications have been reported with Cabozantinib. Stop treatment with Cabozantinib at least 28 days prior to scheduled surgery. Resume Cabozantinib therapy after surgery based on clinical judgment of adequate wound healing. Withhold Cabozantinib in patients with dehiscence or wound healing complications requiring medical intervention.

Hypertension

Cabozantinib treatment results in an increased incidence of treatment-emergent hypertension with Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (modified JNC criteria) stage 1 or 2 hypertension identified in 61% in Cabozantinib-treated patients compared with 30% of placebo-treated patients in the randomized trial. Monitor blood pressure prior to initiation and regularly during Cabozantinib treatment.

Withhold Cabozantinib for hypertension that is not adequately controlled with medical management; when controlled, resume Cabozantinib at a reduced dose. Discontinue Cabozantinib for severe hypertension that cannot be controlled with anti-hypertensive therapy.

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Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) occurred in 1% of Cabozantinib -treated patients. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain or slow healing of the mouth or jaw after dental surgery. Discontinue Cabozantinib for ONJ. Perform an oral examination prior to initiation of Cabozantinib and periodically during Cabozantinib therapy. Advise patients regarding good oral hygiene practices. For invasive dental procedures, withhold Cabozantinib treatment for at least 28 days prior to scheduled surgery, if possible.

Palmar-Plantar Erythrodysesthesia Syndrome

Palmar-plantar erythrodysesthesia syndrome (PPES) occurred in 50% of patients treated with Cabozantinib and was severe (Grade 3) in 13% of patients. Withhold cabozantinib in patients who develop intolerable Grade 2 PPES or Grade 3 PPES until improvement to Grade 1; resume Cabozantinib at a reduced dose.

Proteinuria

Proteinuria was observed in 4 (2%) of patients receiving Cabozantinib, including one with nephrotic syndrome, as compared to none of the patients receiving placebo. Monitor urine protein regularly during Cabozantinib treatment. Discontinue Cabozantinib in patients who develop nephrotic syndrome.

Reversible Posterior Leukoencephalopathy Syndrome

Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in one (<1%) patient. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue Cabozantinib in patients who develop RPLS.

Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, Cabozantinib can cause fetal harm when administered to a pregnant woman. Cabozantinib administration to pregnant animals during organogenesis resulted in embryolethality at exposures below those occurring clinically at the recommended dose, and in increased incidences of skeletal variations in rats and visceral variations and malformations in rabbits. Advise pregnant women of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment with Cabozantinib and for 4 months after the last dose.

SIDE EFFECTS

The most common serious adverse drug reactions in patients treated with Cabozantinib is 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%) were increased AST, increased ALT, lymphopenia, increased ALP, hypocalcemia, neutropenia, thrombocytopenia, hypophosphatemia, and hyperbilirubinemia. Grade 3-4 adverse reactions and laboratory abnormalities which occurred in ≥ 5% of Cabozantinib-treated patients occurring more frequently in the Cabozantinib arm with a between-arm difference of ≥ 2% included, in order of decreasing frequency; diarrhea, PPES, lymphopenia, hypocalcemia, fatigue, hypertension, asthenia, increased ALT, decreased weight, stomatitis, and decreased appetite hypertension and nausea.

DRUG INTERACTIONS

Effect of CYP3A4 Inhibitors

Administration of a strong CYP3A4 inhibitor, ketoconazole to healthy subjects increased singledose 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 coadministered with Cabozantinib.

USE IN SPECIFIC POPULATION

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.

Breast-feeding

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. Fertility There are no data on human fertility. Based on non-clinical safety findings, male and female fertility may be compromised by treatment with cabozantinib. Both men and women should be advised to seek advice and consider fertility preservation before treatment.

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

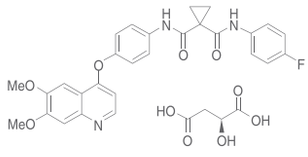
Dosage adjustment is not required in patients with mild or moderate renal impairment. There is no experience with Cabozantinib in patients with severe renal impairment.

OVERDOSE

One case of overdosage was reported in a patient who inadvertently took twice the intended dose (200 mg daily) for nine days. The patient suffered Grade 3 memory impairment, Grade 3 mental status changes, Grade 3 cognitive disturbance, Grade 2 weight loss, and Grade 1 increase in BUN. The extent of recovery was not documented.

DESCRIPTION

Cabozantinib is the (S)-malate salt of Cabozantinib. Cabozantinib (S)-malate is described chemically as N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4 fluorophenyl) cyclopropane1,1-dicarboxamide, (2S) hydroxybutanedioate. The molecular formula is $C_{28}H_{24}FN_3O_5 \bullet C_4H_6O_5$ and the molecular weight is 635.6 Daltons as malate salt. The chemical structure of cabozantinib (S)-malate salt is:



PHARMACEUTICAL INFORMATION

Storage Conditions

Store below 25°C. Keep out of the sight & reach of children. Protect from moisture & light.

How supplied

CABOXEN 20 capsule: Each HDPE container contains 90 capsules each of which contains Cabozantinib 20 mg.

CABOXEN 80 capsule: Each HDPE container contains 30 capsules each of which contains Cabozantinib 80 mg.

Manufactured by

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