Cabanib

Cabozantinib INN 20 mg & 60 mg Capsule

COMPOSITION:

Cabanib-20 mg: Each capsule contains Cabozantinib 20 mg as Cabozantinib (S) Malate INN.

Cabanib-60 mg: Each capsule contains Cabozantinib 60 mg as Cabozantinib (S) Malate INN.

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.

Pharmacokinetics:

Absorption: Following oral administration of Cabozantinib, median time to peak Cabozantinib plasma concentrations (Tmax) ranged from 2 to 5 hours post-dose. Cabozantinib Cmax 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) 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 14C-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: The recommended daily dose of Cabozantinib is 140 mg. It should not be administered with food. Patients should be instructed not to eat for at least 2 hours before and at least 1 hour after taking Cabozantinib. Treatment should be continued until disease progression or unacceptable toxicity occurs. Cabozantinib capsules should be swallowed whole and it should not be opened. A missed dose should not be taken within 12 hours of the next dose. Foods (e.g., grapefruit, grapefruit juice) or nutritional supplements should not be taken that are known to inhibit Cytochrome P450 while taking Cabozantinib. Or, as directed by the registered physician.

Dosage Modifications for Adverse Reactions: Cabozantinib should be withheld 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.

Cabozantinib should be permanently discontinued 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.

SIDE EFFECTS:

- Perforations and Fistula
- Hemorrhage
- Thromboembolic Events
- Wound Complications
- Hypertension
- Osteonecrosis of the Jaw
- Palmar-plantar erythrodysesthesia syndrome
- Proteinuria
- Reversible Posterior Leukoencephalopathy Syndrome

CONTRAINDICATIONS: It is contraindicated in patients with known hypersensitivity to Cabozantinib or any other components of this product.

USE IN PREGNANCY AND LACTATION: It can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. Pregnant women or women of childbearing potential should be advised 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, a lactating woman should be advised not to breastfeed during treatment with Cabozantinib and for 4 months after the final dose.

Females and Males of Reproductive Potential Contraception: Female : Cabozantinib can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should be advised 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.

DRUG INTERACTIONS:

Effect of CYP3A4 Inhibitors: Administration of a strong CYP3A4 inhibitor, Ketoconazole to healthy subjects increased single-dose plasma Cabozantinib exposure by 38%. Taking a strong CYP3A4 inhibitor (e.g., Ketoconazole, Itraconazole, Clarithromycin, Atazanavir, Indinavir, Nefazodone, Nelfinavir, Ritonavir, Saquinavir, Telithromycin, Voriconazole) should be avoided while taking Cabozantinib or the dosage of Cabozantinib should be avoided if concomitant use with strong CYP3A4 inhibitors cannot be avoided. Ingestion of foods (e.g., grapefruit, grapefruit juice) or nutritional supplements should be avoided 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%. Chronic co-administration of strong CYP3A4 inducers should be avoided (e.g., Phenytoin, Carbamazepine, Rifampin, Rifabutin, Rifapentine, Phenobarbital, St. John's Wort) with Cabozantinib or should be increased the dosage of Cabanib 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. Patients should be monitored for increased toxicity when MRP2 inhibitors (e.g., Abacavir, Adefovir, Cidofovir, Furosemide, Lamivudine, Nevirapine, Ritonavir, Probenecid, Saquinavir, and Tenofovir) are co-administered with Cabozantinib.

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. Patients should be monitored for symptoms of perforations and fistulas, including abscess. Cabozantinib should be discontinued in 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%). Cabozantinib should not be administered 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). Cabozantinib should be discontinued in patients who develop an acute myocardial infarction, cerebral infarction, or any other clinically significant arterial thromboembolic complication.

Wound Complications: Wound complications have been reported with Cabozantinib. Treatment with Cabozantinib should be stopped at least 28 days prior to scheduled surgery. Cabozantinib therapy should be resumed after surgery based on clinical judgment of adequate wound healing. It should be withheld 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. Blood pressure should be monitored prior to initiation and regularly during Cabozantinib treatment. It should be withheld for hypertension that is not adequately controlled with medical management; when controlled, it should be resumed at a reduced dose. It should be discontinued for severe hypertension that cannot be controlled with anti-hypertensive therapy.

Osteonecrosis of the Jaw: Osteonecrosis of the jaw (ONJ) occurred in 1% of Cabozantinib- treated patients. Cabozantinib should be discontinued for ONJ. Patients should be advised regarding good oral hygiene practices. For invasive dental procedures, Cabozantinib treatment should be withheld for at least 28 days prior to scheduled surgery, if possible.

Palmar-Plantar Erythrodysesthesia Syndrome: PPES occurred in 50% of patients treated with Cabozantinib and was severe (Grade 3) in 13% of patients. It should be withheld in patients who develop intolerable Grade 2 PPES or Grade 3 PPES until improvement to Grade 1, should be resumed at a reduced dose.

Proteinuria: It was observed in 4 (2%) of patients receiving Cabozantinib, including one with nephrotic syndrome, as compared to none of the patients receiving placebo. Urine protein should be monitored regularly during Cabozantinib treatment. It should be discontinued in patients who develop nephrotic syndrome.

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

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.

STORAGE: Store below 30°C in a cool and dry place, away from sunlight. Keep out of reach of children.

PACKING:

Cabanib-20 : Each box contains 30 capsules in a blister pack.

Cabanib-60 : Each box contains 30 capsules in a blister pack.

Manufactured by
DRUG INTERNATIONAL LTD.
Tongi, Gazipur, Bangladesh