Cabanib-60

Cabozantinib INN
60 mg Tablet

DRUG INTERNATIONAL LTD.

Composition: Each film coated tablet contains Cabozantinib 60 mg as Cabozantinib (S) Malate INN.

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.

Pharmacokinetics:

Absorption: Median time to peak cabozantinib concentrations (Tmax) ranged from 3 to 4 hours post-dose. A 19% increase in the Cmax of Cabozantinib compared to a Cabozantinib capsule formulation was observed following a single 140 mg dose. A less than 10% difference in the AUC was observed between Cabozantinib and a Cabozantinib capsule formulation.

Distribution: The oral volume of distribution (Vz/F) of Cabozantinib is approximately 319 L. Cabozantinib is highly protein bound in human plasma (≥ 99.7%).

Elimination: The predicted terminal half-life is approximately 99 hours and the clearance (CL/F) at steady state is estimated to be 2.2 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 dose of radiolabeled ^{14}C- Cabozantinib 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:

Renal Cell Carcinoma: Cabozantinib is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

Hepatocellular Carcinoma: Cabozantinib is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with Sorafenib.

Dosage and Administration:

Recommended Dosage for Renal Cell Carcinoma: The recommended dosage of Cabozantinib is 60 mg once daily without food until the patient no longer experiences clinical benefit or experiences unacceptable toxicity.

Recommended Dosage for Hepatocellular Carcinoma: The recommended dosage of Cabozantinib is 60 mg once daily without food until disease progression or unacceptable toxicity. Or, as directed by the registered physicians.

- Stop treatment with Cabozantinib at least 28 days prior to scheduled surgery, including dental surgery.
- Do not substitute Cabozantinib tablets with Cabozantinib capsules.
- Do not administer Cabozantinib with food. Administer at least 1 hour before or at least 2 hours after eating.
- Swallow Cabozantinib tablets whole. Do not crush Cabozantinib tablets.
- Do not take a missed dose within 12 hours of the next dose.
- Modify the dose for certain patients with hepatic impairment and for patients taking drugs known to strongly induce or inhibit CYP450.

Side Effects:

- Hemorrhage
- Perforations and Fistulas
- Thrombotic Events
- Hypertension and Hypertensive Crisis
- Diarrhea
- Palmar-plantar Erythrodysesthesia
- Proteinuria
- Osteonecrosis of the Jaw
- Wound Complications
- Reversible Posterior Leukoencephalopathy Syndrome

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

Use in Pregnancy and Lactation: 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.

Lactation: There is no information regarding the presence of Cabozantinib or its metabolites in human milk, or their effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in breastfed children, women should be advised not to breastfed during treatment with Cabozantinib and for 4 months after the final dose.

Females and Males of Reproductive Potential:

Contraception: Cabozantinib can cause fetal harm when administered to a pregnant woman.

Females: 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 established.

Drug Interactions: Effects of Other Drugs on Cabozantinib:

Strong CYP3A4 Inhibitors: Coadministration of a Cabozantinib capsule formulation with a strong CYP3A4 inhibitor increased the exposure of Cabozantinib, which may increase the risk of exposure-related adverse reactions. Avoid coadministration of Cabozantinib with strong CYP3A4 inhibitors. Reduce the dosage of Cabozantinib if coadministration with strong CYP3A4 inhibitors cannot be avoided. Avoid grapefruit or grapefruit juice which may also increase exposure of Cabozantinib.

Strong CYP3A Inducers: Coadministration of a Cabozantinib capsule formulation with a strong CYP3A4 inducer decreased the exposure of Cabozantinib, which may reduce efficacy. Avoid coadministration of Cabozantinib with strong CYP3A4 inducers. Increase the dosage of Cabozantinib if coadministration with strong CYP3A4 inducers cannot be avoided. Avoid St. John's Wort which may also decrease exposure of Cabozantinib.

Precautions:

Hemorrhage: Severe and fatal hemorrhages occurred with Cabozantinib. Discontinue Cabozantinib for Grade 3 or 4 hemorrhage. Do not administer Cabozantinib to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Perforations and Fistulas: Fistulas, including fatal cases, occurred in 1% of Cabozantinib -treated patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of Cabozantinib -treated patients. Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue Cabozantinib in patients who experience a fistula which cannot be appropriately managed or a GI perforation.

Thrombotic Events: Cabozantinib increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism occurred in 2% of Cabozantinib -treated patients. Fatal thrombotic events occurred in Cabozantinib-treated patients. Discontinue Cabozantinib in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

Hypertension and Hypertensive Crisis: Cabozantinib can cause hypertension, including hypertensive crisis. Do not initiate Cabozantinib in patients with uncontrolled hypertension. Monitor blood pressure 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 or for hypertensive crisis.

Diarrhea: Diarrhea occurred in 63% of patients treated with Cabozantinib. Withhold Cabozantinib until improvement to Grade 1 and resume Cabozantinib at a reduced dose for intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.

Palmar-Plantar Erythrodysesthesia: Palmar-plantar erythrodysesthesia (PPE) occurred in 44% of patients treated with Cabozantinib. Withhold Cabozantinib until improvement to Grade 1 and resume Cabozantinib at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Proteinuria: Proteinuria was observed in 7% of patients receiving Cabozantinib. Monitor urine protein regularly during Cabozantinib treatment. Discontinue Cabozantinib in patients who develop nephrotic syndrome.

Osteonecrosis of the Jaw: Osteonecrosis of the jaw (ONJ) occurred in <1% of patients treated with Cabozantinib. 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. Perform an oral examination prior to initiation of Cabozantinib and periodically during Cabozantinib. Advise patients regarding good oral hygiene practices. Withhold Cabozantinib for at least 28 days prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold Cabozantinib for development of ONJ until complete resolution.

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

Reversible Posterior Leukoencephalopathy Syndrome: Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, can occur with Cabozantinib. 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. 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.

Overdose: One case of overdosage was reported following administration of another formulation of Cabozantinib; a patient inadvertently took twice the intended dose for 9 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: Each box contains 30 tablets in a blister pack.