165mm

155mm

Palmar-Plantar Erythrodysesthesia Syndrome:
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.

Reversible Posterior Leukoencephalopathy Syndrome:
Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in the Cabozantinib ib clinical program. 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 embryo lethality 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

EFFECT OF OTHER DRUGS ON CABOZANTINIB
Strong CYP3A4 inhibitors: Concomitant use of CABOZANTINIB with a strong CYP3A4 inhibitor increased the exposure of Cabozantinib compared to the use of CABOZANTINIB alone. Reduce the CABOZANTINIB dosage if coadministration cannot be avoided.
Strong or moderate CYP3A4 inducers: Increase the CABOZANTINIB dosage if coadministration cannot be avoided.

OVERDOSAGE
There is no specific treatment for cabozantinib overdose and possible symptoms of overdose have not been established. In the event of suspected overdose, cabozantinib should be withheld and supportive care instituted. Metabolic clinical laboratory parameters should be monitored at least weekly or as deemed clinically appropriate to assess any possible changing trends. Adverse reactions associated with overdose are to be treated symptomatically.

HOW SUPPLIED
Cabozantin 20mg tablet is available in blister packs of 1x10's ,2x10's & 3x10's & 9x10's.
Cabozantin 40mg tablet is available in blister packs of 1x10's ,2x10's & 3x10's.
Cabozantin 60mg tablet is available in blister packs of 1x10's ,2x10's & 3x10's.

Dosage: As directed by the physician.

Instructions: Store at 25°C, (Excursions permitted between 15°C to 30°C). Protect from sunlight & moisture. Keep out of the reach of children.
To be dispensed on the prescription of a registered medical practitioner only.

خوراک : ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات : دوا کو ۲۵ ڈگری سینٹی گریڈ درجہ حرارت پر رکھیں۔
(درجہ حرارت کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے) ۔
دھوپ اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

Kaizen Pharmaceuticals (Pvt.) Ltd.

Manufactured by:
Kaizen Pharmaceuticals (Pvt.) Ltd.
E-127-129, North Western Industrial Zone,
Bin Qasim, Karachi-75020, Pakistan.

Cabozantin

(Cabozantinib S-Malate)

20mg ,40mg & 60mg Tablet

کیبوزینٹن

(کیبوزینٹینب ایس۔میلیٹ)

Composition: ۲۰ ملی گرام، ۴۰ ملی گرام اور ۶۰ ملی گرام گولیاں

Each film coated tablet contains:
Cabozantinib (S)-Malate Eq. to Cabozantinib..... 20mg

Each film coated tablet contains:
Cabozantinib (S)-Malate Eq. to Cabozantinib..... 40mg

Each film coated tablet contains:
Cabozantinib (S)-Malate Eq. to Cabozantinib 60mg

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.

Pharmacodynamics:
The exposure-response or –safety relationship for Cabozantinib is unknown.

Cardiac Electrophysiology
The effect of orally administered Cabozantinib on QTc interval was evaluated in a randomized, double-blinded, placebo-controlled study in patients with medullary thyroid cancer administered a dose of 140 mg. A mean increase in QTcB 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 Cabozantinibtreated patients in this study had a confirmed QTcF > 500 ms nor did any Cabozantinib-treated patients in the RCC study (at a dose of 60 mg)

PHARMACOKINETICS
Absorption
Following oral administration of Cabozantinib, median time to peak Cabozantinib plasma concentrations (Tmax) ranged from 2 to 3 hours post-dose.

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 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 advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

SPECIAL POPULATION
Pregnancy Risk Summary
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. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Lactation Risk Summary:
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.

Pediatric Use:
The safety and effectiveness of CABOZANTINIB in pediatric patients have not been studied.

Geriatric Use:
No differences in safety or efficacy were observed between older and younger patients.

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

Hepatic Impairment:
Increased exposure to Cabozantinib has been observed in patients with mild to moderate hepatic impairment. Reduce the CABOZANTINIB dose 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.

DOSAGE & ADMINISTRATION
Do not substitute CABOZANTINIB tablets with Cabozantinib capsules.

The recommended daily dose of CABOZANTINIB is 60 mg. 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 patient no longer experiences clinical benefit or experiences unacceptable toxicity.
Swallow CABOZANTINIB tablets whole. Do not crush CABOZANTINIB tablets.
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 during CABOZANTINIB treatment.

Dosage Adjustments
For Patients Undergoing Surgery
Stop treatment with CABOZANTINIB at least 28 days prior to scheduled surgery, including dental surgery.

ROUTE OF ADMINISTRATION
For oral administration only.

ADVERSE REACTIONS
The following serious adverse reactions are discussed elsewhere in the label:
Hemorrhage.
GI Perforations and Fistulas.
Thrombotic Events.
Hypertension and Hypertensive Crisis.
Diarrhea.
Palmar-plantar erythrodysesthesia syndrome.
Reversible Posterior Leukoencephalopathy Syndrome.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Hemorrhage
Severe hemorrhage occurred with CABOZANTINIB. Do not administer CABOZANTINIB to patients that have or are at risk for severe hemorrhage.

GI Perforations and Fistulas
Monitor patients for symptoms of fistulas and perforations. Discontinue CABOZANTINIB in patients who experience a fistula which cannot be appropriately managed or a GI perforation.

Thrombotic Events:
CABOZANTINIB treatment results in an increased incidence of thrombotic events.
Discontinue CABOZANTINIB in patients who develop an acute myocardial infarction or any other arterial thromboembolic complication.

Hypertension and Hypertensive Crisis:
CABOZANTINIB treatment results in an increased incidence of treatment-emergent hypertension. 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. Discontinue CABOZANTINIB if there is evidence of hypertensive crisis or severe hypertension despite optimal medical management.

Diarrhea:
Withhold CABOZANTINIB in patients who develop intolerable Grade 2 diarrhea or Grade 3-4 diarrhea that cannot be managed with standard antidiarrheal treatments until improvement to Grade 1; resume CABOZANTINIB at a reduced dose.