Cazar

Cabozantinib

Julphar Bangladesh | جلفار بنغلاديش

Composition:

Cazar 20 Capsule: Each capsule contains Cabozantinib S-Malate INN equivalent to Cabozantinib 20 mg.

Cazar 80 Capsule: Each capsule contains Cabozantinib S-Malate INN equivalent to Cabozantinib 80 mg.

Description:

Cazar 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) cyclopropane 1, 1-dicarboxamide, (2S)-hydroxybutanedioate. The molecular formula is C28H24FN3O5.C4H6O5 and the molecular weight is 635.6 g/mol.

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, and TIE-2. These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, and maintenance of the tumor microenvironment.

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. The predicted effective half-life is approximately 55 hours, the oral volume of distribution (V/F) is approximately 349 L, and the clearance (CL/F) at steady-state is estimated to be 4.4 L/hr.

Absorption and Distribution

Following oral administration of Cazar, median time to peak cabozantinib plasma concentrations (Tmax) ranged from 2 to 5 hours post-dose. Repeat daily dosing of Cazar 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. Cabozantinib is highly protein bound in human plasma (≥ 99.7%). A high-fat meal increased Cmax and AUC values by 41% and 57%, respectively relative to fasted conditions in healthy subjects administered a single 140 mg oral Cazar dose.

Metabolism and Elimination

Cabozantinib is a substrate of CYP3A4 in vitro. Inhibition of CYP3A4 reduced the formation of the XL184 N-oxide metabolite by >80%. Inhibition of CYP2C9 had a minimal effect on cabozantinib metabolite formation (i.e., a<20% reduction). Inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP2E1 had no effect on cabozantinib metabolite formation.

Within a 48 days' collection period after a single dose of 14C-cabozantinib in healthy subjects, approximately 81% of total administered radioactivity was recovered with 54% in feces and 27% in urine.

Indications:

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

Dose and Administration:

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

Dosage Adjustment:

For Adverse Reactions Withhold Cazar 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 Cazar permanently discontinue Cazar 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 with Hepatic Impairment Cazar is not recommended for use in patients with moderate and severe hepatic impairment.

In Patients Taking CYP3A4 Inhibitors Avoid the use of concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) in patients receiving Cazar.

For patients who require treatment with a strong CYP3A4 inhibitor, reduce the daily Cazar 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 Taking Strong CYP3A4 Inducers Avoid the chronic use of concomitant strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) if alternative therapy is available.

Do not ingest foods or nutritional supplements (e.g., St. John's Wort (Hypericum perforatum)) that are known to induce cytochrome P450 activity.

For patients who require treatment with a strong CYP3A4 inducer, increase the daily Cazar 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 Cazar should not exceed 180 mg.

Special Population:

Pregnancy

Pregnancy Category "D". Based on its mechanism of action, Cazar can cause fetal harm when administered to a pregnant woman. Cabozantinib was embryolethal in rats at exposures below the recommended human dose, with increased incidences of skeletal variations in rats and visceral variations and malformations in rabbits. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nursing Mother

It is unknown whether cabozantinib or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and

because of the potential for serious adverse reactions in nursing infants from Cazar, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

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

Geriatric Use

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

Females and Males of Reproductive Potential

Contraception: Use effective contraception during treatment with Cazar and up to 4 months after completion of therapy.

Infertility: There are no data on the effect of Cazar on human fertility. Cabozantinib impaired male and female fertility in animal studies.

Hepatic Impairment

Cabozantinib pharmacokinetics has not been studied in patients with hepatic impairment. There are limited data in patients with liver impairment (serum bilirubin greater than 1.5 times the upper limit of normal). Cazar is not recommended for use in patients with moderate or severe hepatic impairment, as safety and efficacy have not been established.

Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment. There is no experience with Cazar in patients with severe renal impairment.

Overdosage:

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.

Contraindication:

Hypersensitivity to the active substance or to any of the excipients.

Warnings and Precautions:

Perforations and Fistulas

Gastrointestinal (GI) perforations and fistulas were reported in 3% and 1% of Cazar treated patients, respectively. All were serious and one GI fistula was fatal (< 1%). Non-GI fistulas including tracheal/ esophageal were reported in 4% of Cazar-treated patients. Two (1%) of these were fatal. Monitor patients for symptoms of perforations and fistulas. Discontinue Cazar in patients who experience a perforation or a fistula.

Hemorrhage

Serious and sometimes fatal hemorrhage occurred with Cazar. The incidence of Grade ≥3 hemorrhagic events was higher in Cazar-treated patients compared with placebo (3% vs. 1%). Do not administer Cazar to patients with a recent history of hemorrhage or hemoptysis.

Thrombotic Events

Cazar treatment results in an increased incidence of thrombotic events (venous thromboembolism: 6% vs. 3% and arterial thromboembolism: 2% vs. 0% in Cazar-treated and placebo- treated patients, respectively). Discontinue Cazar in patients who develop an acute myocardial infarction or any other clinically significant arterial thromboembolic complication.

Wound Complications

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

Hypertension

Cazar 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 Cazar-treated patients compared with 30% of placebo-treated patients in the randomized trial. Monitor blood pressure prior to initiation and regularly during Cazar treatment. Withhold Cazar for hypertension that is not adequately controlled with medical management; when controlled, resume Cazar at a reduced dose. Discontinue Cazar for severe hypertension that cannot be controlled with anti-hypertensive therapy.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) occurred in 1% of Cazar-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. Perform an oral examination prior to initiation of Cazar and periodically during Cazar therapy. Advise patients regarding good oral hygiene practices. For invasive dental procedures, withhold Cazar treatment for at least 28 days prior to scheduled surgery, if possible.

Proteinuria

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

Adverse Reactions:

The following serious adverse reactions are discussed elsewhere in the label:

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

Pharmaceutical Information:

Storage Condition

Store in a cool and dry place below 30° C, protect from light. Keep out of the reach of children.

How Supplied

Cazar 20 Capsule**:** Each box contains 90 capsules and one packet silica gel in a sealed plastic container.

Cazar 80 Capsule**:** Each box contains 30 capsules and one packet silica gel in a sealed plastic container.

Manufactured by:
Julphar Bangladesh Ltd.
Sreepur, Gazipur, Bangladesh.