Capmaxen

Capmatinib 200 mg tablets

Everest

COMPOSITION

Capmaxen tablet: Each film coated tablet contains Capmatinib Hydrochloride INN equivalent to Capmatinib 200 mg.

PHARMACOLOGY

Mechanism of Action:

Capmatinib is a kinase inhibitor that targets MET, including the mutant variant produced by exon 14 skipping. MET exon 14 skipping results in a protein with a missing regulatory domain that reduces its negative regulation leading to increased downstream MET signaling. Capmatinib inhibited cancer cell growth driven by a mutant MET variant lacking exon 14 at clinically achievable concentrations and demonstrated anti-tumor activity in murine tumor xenograft models derived from human lung tumors with either a mutation leading to MET exon 14 skipping or MET amplification. Capmatinib inhibited the phosphorylation of MET triggered by binding of hepatocyte growth factor or by MET amplification, as well as MET mediated phosphorylation of downstream signaling proteins and proliferation and survival of MET-dependent cancer cells.

Pharmacokinetic properties

Capmatinib exposure (AUC0-12h and Cmax) increased approximately proportionally over a dose range of 200 mg (0.5 times the recommended dosage) to 400 mg. Capmatinib reached steady-state by day 3 following twice daily dosing, with a mean (% coefficient of variation [%CV]) accumulation ratio of 1.5 (41%).

Absorption

After administration of Capmatinib 400 mg orally in patients with cancer, Capmatinib peak plasma concentrations (Cmax) were reached in approximately 1 to 2 hours (Tmax). The absorption of Capmatinib after oral administration is estimated to be greater than 70%.

Effect of food

A high-fat meal (containing approximately 1000 calories and 50% fat) in healthy subjects increased capmatinib AUC0-INF by 46% with no change in Cmax compared to under fasted conditions. A low-fat meal (containing approximately 300 calories and 20% fat) in healthy subjects had no clinically meaningful effect on capmatinib exposure. When Capmatinib was administered at 400 mg orally twice daily in cancer patients, exposure (AUC0-12h) was similar after administration of Capmatinib with food and under fasted conditions.

Distribution

Capmatinib plasma protein binding is 96%, independent of Capmatinib concentration. The apparent mean volume of distribution at steady-state is 164 L.

The blood-to-plasma ratio was 1.5, but decreased at higher concentrations to 0.9

Elimination

The effective elimination half-life of Capmatinib is 6.5 hours. The mean (%CV) steady-state apparent clearance of Capmatinib is 24 L/hr (82%).

Metabolism

Capmatinib is primarily metabolized by CYP3A4 and aldehyde oxidase.

Excretion

Following a single oral administration of radiolabeled-Capmatinib to healthy subjects, 78% of the total radioactivity was recovered in feces with 42% as unchanged and 22% was recovered in urine with negligible as unchanged.

Specific Populations

No clinically significant effects on the pharmacokinetic parameters of Capmatinib were identified for the following covariates assessed: age (26 to 90 years), sex, race (White, Asian, Native American, Black, unknown), body weight (35 to 131 kg), mild to moderate renal impairment (baseline CLcr 30 to 89 mL/min by Cockcroft-Gault) and mild, moderate or severe hepatic impairment (Child-Pugh classification). The effect of severe renal impairment (baseline CLcr 15 to 29 mL/min) on Capmatinib pharmacokinetics has not been studied.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Strong CYP3A Inhibitors: Coadministration with itraconazole (a strong CYP3A inhibitor) increased Capmatinib AUC0-INF by 42% with no change in capmatinib Cmax.

Strong CYP3A Inducers: Coadministration with rifampicin (a strong CYP3A inducer) decreased capmatinib AUC0-INF by 67% and decreased Cmax by 56%.

Moderate CYP3A Inducers: Coadministration with efavirenz (a moderate CYP3A inducer) was predicted to decrease capmatinib AUC0-12h by 44% and decrease Cmax by 34%.

Proton Pump Inhibitors: Coadministration with rabeprazole (a proton pump inhibitor) decreased capmatinib AUC0-INF by 25% and decreased Cmax by 38%.

Substrates of CYP Enzymes: Coadministration of capmatinib increased caffeine (a CYP1A2 substrate) AUC0-INF by 134% with no change in its Cmax. Coadministration of Capmatinib had no clinically meaningful effect on exposure of midazolam (a CYP3A substrate).

P-gp Substrates: Coadministration of Capmatinib increased digoxin (a P-gp substrate) AUC0-INF by 47% and increased Cmax by 74%.

BCRP Substrates: Coadministration of Capmatinib increased rosuvastatin (a BCRP substrate) AUC0-INF by 108% and increased Cmax by 204%.

In Vitro Studies

Transporter Systems: Capmatinib is a substrate of P-gp, but not a substrate of BCRP or MRP2. Capmatinib reversibly inhibits MATE1 and MATE2K, but does not inhibit OATP1B1, OATP1B3, OCT1, OAT1, OAT3, or MRP2.

INDICATIONS AND USAGE

Capmatinib is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA approved test.

DOSAGE AND ADMINISTRATION

Patient Selection

Select patients for treatment with Capmatinib based on the presence of a mutation that leads to MET exon 14 skipping in tumor or plasma specimens. If a mutation that leads to MET exon 14 skipping is not detected in a plasma specimen, test tumor tissue if feasible.

Recommended Dose

The recommended dosage of Capmatinib is 400 mg orally twice daily with or without food.

Swallow Capmatinib tablets whole. Do not break, crush or chew the tablets.

If a patient misses or vomits a dose, instruct the patient not to make up the dose, but to take the next dose at its scheduled time.

Dosage Modifications for Adverse Reactions

The recommended dose reductions for the management of adverse reactions are listed in Table 1.

Table 1: Recommended Capmatinib Dose Reductions for Adverse Reactions

Dose Reduction	Dose and Schedule
First	300 mg orally twice daily
Second	200 mg orally twice daily

Permanently discontinue Capmatinib in patients who are unable to tolerate 200 mg orally twice daily.

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CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Interstitial Lung Disease (ILD)

Immediately withhold Capmatinib in patients with suspected ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis are identified.

Hepatotoxicity

Monitor liver function tests (including ALT, AST, and total bilirubin) prior to the start of Capmatinib, every 2 weeks during the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients who develop increased transaminases or bilirubin. Based on the severity of the adverse reaction, withhold, dose reduce, or permanently discontinue Capmatinib.

Pancreatic Toxicity

Monitor amylase and lipase at baseline and regularly during treatment with Capmatinib. Based on the severity of the adverse drug reaction, temporarily withhold, dose reduce, or permanently discontinue Capmatinib.

Risk of Photosensitivity

Advise patients to limit direct ultraviolet exposure during treatment with Capmatinib.

Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, Capmatinib can cause fetal harm when administered to a pregnant woman.

SIDE EFFECTS

- Lung or breathing problems
- Liver problems.
- Pancreas problems.
- Swelling of your hands or feet
- Nausea
- Muscle or bone pain
- Tiredness and weakness
- Vomiting
- Trouble breathing
- Cough
- Loss of appetite
- Changes in certain blood tests

DRUG INTERACTIONS

Effect of Other Drugs on Capmatinib

Strong CYP3A Inhibitors

Closely monitor patients for adverse reactions during coadministration of Capmatinib with strong CYP3A inhibitors.

Strong and Moderate CYP3A Inducers

Avoid coadministration of Capmatinib with strong and moderate CYP3A inducers.

Effect of Capmatinib on Other Drugs

CYP1A2 Substrates

Coadministration of Capmatinib increased the exposure of a CYP1A2 substrate, which may increase the adverse reactions of these substrates.

P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) Substrates

Coadministration of Capmatinib increased the exposure of a P-gp substrate and a BCRP substrate, which may increase the adverse reactions of these substrates.

MATE1 and MATE2K Substrates

Coadministration of Capmatinib may increase the exposure of MATE1 and MATE2K substrates, which may increase the adverse reactions of these substrates.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Capmatinib can cause fetal harm when administered to a pregnant woman. There are no available data on Capmatinib use in pregnant women. Advise pregnant women of the potential risk to a fetus.

Lactation

Risk Summary

Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with Capmatinib and for 1 week after the last dose.

Females and Males of Reproductive Potential

Based on animal data, Capmatinib can cause malformations at doses less than the human exposure based on AUC at the 400 mg twice daily clinical dose.

Pregnancy Testing

Verify pregnancy status for females of reproductive potential prior to starting treatment with Capmatinib.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with Capmatinib and for 1 week after the last dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with Capmatinib and for 1 week after the last dose.

Pediatric Use

Safety and effectiveness of Capmatinib in pediatric patients have not been established.

Geriatric Use

In GEOMETRY mono-1, 61% of the 373 patients were 65 years or older and 18% were 75 years or older. No overall differences in the safety or effectiveness were observed between these patients and younger patients.

Renal Impairment

No dosage adjustment is recommended in patients with mild (baseline creatinine clearance [CLcr] 60 to 89 mL/min by Cockcroft-Gault) or moderate renal impairment (CLcr 30 to 59 mL/min). Capmatinib has not been studied in patients with severe renal impairment (CLcr 15 to 29 mL/min).

PHARMACEUTICAL INFORMATION

Storage Condition

Store below 25°C, in a cool and dry place. Keep away from light. Keep out of the reach of children.

How Supplied

Capmaxen tablet: Each HDPE container contains 56 film coated tablets (each tablet contains 200 mg Capmatinib) a silica gel desiccant and polyester coil with a child-resistant closure.

Manufactured by

Everest Pharmaceuticals Ltd.

BSCIC I/A, Kanchpur, Narayanganj, Bangladesh

www.everestpharmabd.com

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