FRUQUIN

Fruquintinib INN

Everest

COMPOSITION

FRUQUIN capsule: Each capsule contains Fruquintinib INN 5 mg.

PHARMACOLOGY

Fruquintinib is a small molecule kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3 with IC_{50} values of 33, 35, and 0.5 nM, respectively. In vitro studies showed fruquintinib inhibited VEGF-mediated endothelial cell proliferation and tubular formation. In vitro and in vivo studies showed Fruquintinib inhibited VEGF-induced VEGFR-2 phosphorylation. In vivo studies showed fruquintinib inhibited tumor growth in a tumor xenograft mouse model of colon cancer.

INDICATION

Fruquintinib is a kinase inhibitor indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with Fluoropyrimidine-, Oxaliplatin-, and Irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type and medically appropriate, an anti-EGFR therapy.

DOSAGE AND ADMINISTRATION

The recommended dose of Fruquintinib is 5 mg orally once daily for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity. Take Fruquintinib with or without food at approximately the same time each day.

Dosage Modifications for Adverse Reactions

The recommended dose reductions for adverse reactions are provided in Table 1.

Table 1: Recommended Dose Reductions for Fruquintinib

Dose Level	Fruquintinib Dose
First dose reduction	4 mg orally once daily
Second dose reduction	3 mg orally once daily

Permanently discontinue Fruquintinib in patients unable to tolerate 3 mg orally once daily. The recommended dosage modifications for adverse reactions are provided in Table 2.

Table 2: Recommended Dosage Modifications for Fruquintinib

Adverse Reaction	Severity[1]	Fruquintinib Dosage Modification
Hypertension	Grade 3	• Withhold Fruquintinib for Grade 3 hypertension that persists despite optimal anti-hypertensive therapy. • If hypertension fully resolves or recovers to Grade 1, resume at the next lower dose level.
	Grade 4	Permanently discontinue Fruquintinib
Hemorrhagic Events	Grade 2	• Withhold Fruquintinib until bleeding fully resolves or recovers to Grade 1. • Resume at the next lower dose level.
	Grade 3 or Grade 4	Permanently discontinue Fruquintinib.
Hepatotoxicity	Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 3 times upper limit of normal (ULN) with total bilirubin less than or equal to 2 times ULN	• Withhold Fruquintinib and monitor AST/ALT and total bilirubin until resolution to Grade 1 or baseline. • Resume at the next lower dose level.
	ALT or AST greater than 3 times ULN with concurrent total bilirubin greater than 2 times ULN (in the absence of cholestasis or hemolysis)	Permanently discontinue Fruquintinib.
	AST or ALT greater than 20 times ULN or bilirubin greater than 10 times ULN	Permanently discontinue Fruquintinib.
Proteinuria	2 grams or greater proteinuria in 24 hours	• Withhold Fruquintinib until proteinuria fully resolves or is <1 gram/24 hours. • Upon recovery, resume at the next lower dose level. Permanently discontinue Fruquintinib for nephrotic syndrome or if proteinuria does not recover to <1 gram/24 hours.
Palmar-plantar erythrodysesthesia (PPE)	Grade 2	• Withhold Fruquintinib and initiate supportive treatment. • If toxicity fully resolves or recovers to Grade 1, resume at the same dose level.
	Grade 3	• Withhold Fruquintinib and initiate supportive treatment. • If toxicity fully resolves or recovers to Grade 1, resume at the next lower dose level.
Other Adverse Reactions	Grade 3	• Withhold Fruquintinib. • If toxicity fully resolves or recovers to Grade 1, resume at the next lower dose level.
	Grade 4	Discontinue Fruquintinib. Consider resuming Fruquintinib at the next lower dose level only if the toxicity is non-life threatening and fully resolves or recovers to Grade 1 and the potential benefit outweighs the risks.

[1] Severity as defined by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

CONTRAINDICATION

None.

Adverse Reaction

Most common adverse reactions (incidence ≥20%) are hypertension, palmar-plantar erythrodysesthesia, proteinuria, dysphonia, abdominal pain, diarrhea, and asthenia.

WARNINGS AND PRECAUTION

Hypertension

Control blood pressure prior to treatment and monitor during treatment. Manage with anti-hypertensive medications and adjustment of the dose of Fruquintinib, if necessary. Withhold, dose reduce, or permanently discontinue based on severity of hypertension.

Hemorrhagic Events

Closely monitor patients who are at risk for bleeding. Withhold, reduce dose, or permanently discontinue Fruquintinib based on severity and persistence of hemorrhage.

Infections
Monitor for infection during treatment and withhold Fruquintinib during active infections. Do not start Fruquintinib in patients with active infections.

Gastrointestinal (GI) Perforation
Periodically monitor for GI perforation. Permanently discontinue Fruquintinib in patients who develop GI perforation or fistula.

Hepatotoxicity
Monitor liver laboratory tests prior to the start of Fruquintinib and periodically during treatment. Withhold, reduce the dose, or permanently discontinue based on severity.

Proteinuria
Monitor urine protein. Discontinue Fruquintinib for nephrotic syndrome.

Palmar-Plantar Erythrodysesthesia
Withhold Fruquintinib based on severity.

Posterior Reversible Encephalopathy Syndrome (PRES)
Immediately discontinue Fruquintinib if PRES is suspected and confirmed via Magnetic Resonance Imaging (MRI).

Impaired Wound Healing
Withhold Fruquintinib for 2 weeks before major surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Fruquintinib after resolution of wound healing complications has not been established.

Arterial Thromboembolic Events
Initiation of Fruquintinib in patients with a recent history of thromboembolic events should be carefully considered. Discontinue Fruquintinib in patients who develop arterial thromboembolism.

Allergic Reactions to FD&C Yellow No. 5 (Tartrazine) and No. 6 (Sunset Yellow FCF)
Contains FD&C Yellow No. 5 (Tartrazine) and No. 6 (Sunset Yellow FCF) as color additives, which may cause allergic reactions (including bronchial asthma) in certain susceptible patients.

Embryo-Fetal Toxicity
Can cause fetal harm. Advise patients of reproductive potential of the potential risk to the fetus and to use effective contraception.

USE IN SPECIFIC POPULATIONS

Pregnancy
Fruquintinib may harm fetuses based on animal studies. Rat studies showed birth defects and embryo death at doses below human levels. No human pregnancy data exists. Pregnant women should be informed of risks. In the U.S., background risk is 2-4% for birth defects and 15-20% for miscarriage. Rat studies showed fetal abnormalities at ≥0.1 mg/kg and increased embryo loss at 0.25 mg/kg (0.2 and 0.5 times human dose, respectively).

Lactation
Advise not to breastfeed.

Females and Males of Reproductive Potential
Pregnancy Testing
Verify pregnancy status of females of reproductive potential prior to initiating Fruquintinib.

Contraception
Females and Males
Females of childbearing potential and males with female partners of childbearing potential should use effective contraception during treatment and for 2 weeks after the last dose of Fruquintinib.

Pediatric Use
The safety and efficacy of Fruquintinib in patients younger than 18 years of age have not been established.

Hepatic Impairment
No dosage adjustment is recommended for patients with mild hepatic impairment (total bilirubin less than or equal to the ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST. Fruquintinib has not been sufficiently studied in patients with moderate hepatic impairment (total bilirubin greater than 1.5 times and less than 3 times ULN and any AST). Fruquintinib is not recommended for use in patients with severe hepatic impairment (total bilirubin greater than 3 times ULN and any AST).

OVERDOSE
In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

DRUG INTERACTIONS

Strong CYP3A Inducers
Avoid concomitant use of drugs that are strong CYP3A inducers with Fruquintinib. Concomitant use with a strong CYP3A inducer may decrease Fruquintinib C_{max} and AUC, which may reduce the efficacy of Fruquintinib.

Moderate CYP3A Inducers
If possible, avoid concomitant use of drugs that are moderate CYP3A inducers with Fruquintinib. If it is not possible to avoid concomitant use of a moderate CYP3A inducer and Fruquintinib, continue to administer Fruquintinib at the recommended dosage.

Concomitant use with a moderate CYP3A inducer may decrease Fruquintinib C_{max} and AUC, which may reduce the efficacy of Fruquintinib.

PHARMACEUTICAL INFORMATION

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

How Supplied
FRUQUIN capsule: Each HDPE container contains 21 capsules, a silica gel desiccant and polyester coil with child resistant closure.

Manufactured by
Everest Pharmaceuticals Ltd.
BSCIC I/A, Kanchpur, Narayanganj, Bangladesh
www.everestpharmabd.com

1901000232