MoboXen

Mobocertinib 40 mg capsules

Everest

COMPOSITION

Moboxen capsule: Each capsule contains Mobocertinib Succinate INN equivalent to Mobocertinib 40 mg.

PHARMACOLOGY

Mechanism of Action

Mobocertinib is a kinase inhibitor of the epidermal growth factor receptor (EGFR) that irreversibly binds to and inhibits EGFR exon 20 insertion mutations at lower concentrations than wild type (WT) EGFR. Two pharmacologically-active metabolites (AP32960 and AP32914) with similar inhibitory profiles to Mobocertinib have been identified in the plasma after oral administration of Mobocertinib. In vitro, Mobocertinib also inhibited the activity of other EGFR family members (HER2 and HER4) and one additional kinase (BLK) at clinically relevant concentrations (IC_{50} values <2 nM).

Pharmacokinetic properties

After single and multiple-dose administration, combined molar C_{max} and AUC_{0-24h} of Mobocertinib and its active metabolites, AP32960 and AP32914, was dose-proportional over the dose range of 5 to 180 mg once daily (0.03 to 1.1 times the approved recommended dosage). No clinically meaningful accumulation was observed after administration of Mobocertinib 160 mg once daily based on the AUC ratio of Mobocertinib.

Absorption

The median (min, max) time to peak concentration (T_{max}) of Mobocertinib is 4 hours (1, 8 hours). The mean (%CV) absolute bioavailability is 37% (50%).

Effect of food

No clinically meaningful differences in the combined molar AUC and C_{max} of Mobocertinib, AP32960, and AP32914 were observed following administration of a high-fat meal (approximately 900 to 1000 calories, with 150 calories from protein, 250 calories from carbohydrate and 500 to 600 calories from fat) or a low fat-meal (approximately 336 calories, with 37 calories from protein, 253 calories from carbohydrate, and 46 calories from fat) compared to administration after an overnight fast.

Distribution

Mobocertinib was bound to human plasma proteins in a concentration independent manner in vitro from 0.5 to 5.0 μ M. The mean (standard deviation) bound fraction was 99.3% (0.11%) for Mobocertinib, 99.5% (0.16%) for AP32960 and 98.6% (0.36%) for AP32914 in vitro.

Elimination

The mean (%CV) plasma elimination half-life of Mobocertinib was 18 hours (21%) at steady-state. The mean apparent oral clearance (CL/F) (%CV) of Mobocertinib was 138 L/hr (47%) at steady-state. The mean (%CV) plasma elimination half-life of AP32960 was 24 hours (20%) at steady-state. The mean apparent oral clearance (CL/F) (%CV) of AP32960 was 149 L/hr (36%) at steady-state. The mean (%CV) plasma elimination half-life of AP32914 was 18 hours (21%) at steady-state. The mean apparent oral clearance (CL/F) (%CV) of AP32914 was 159 L/hr (52%) at steady-state.

Metabolism

Mobocertinib is primarily metabolized by CYP3A. The two active metabolites, AP32960 and AP32914, are equipotent to Mobocertinib and account for 36% and 4% of the combined molar AUC, respectively.

Excretion

Following administration of a single 160 mg oral dose of radiolabeled Mobocertinib, approximately 76% of the dose was recovered in feces (approximately 6% as unchanged Mobocertinib) and approximately 4% was recovered in urine (approximately 1% as unchanged Mobocertinib). The percentage of the administered dose recovered in feces and urine for AP32960 was approximately 12% and 1%, respectively. The metabolite AP32914 was below the detection limit in urine and feces.

Specific Populations

No clinically meaningful differences in the pharmacokinetics of Mobocertinib were observed based on age (18 to 86 years), race (White, Black, Asian), sex, body weight (37.3 to 132 kg), mild-to-moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2 by MDRD), or mild (total bilirubin ≤ ULN and AST > ULN or total bilirubin >1 to 1.5 times ULN and any AST)-to-moderate (total bilirubin ≥1.5 to 3 times ULN and any AST) hepatic impairment. The effect of severe (eGFR <30 mL/min/1.73 m^2) renal impairment and severe (total bilirubin >3 times ULN and any AST) hepatic impairment on Mobocertinib pharmacokinetics is unknown.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Effect of CYP3A Inhibitors on Mobocertinib: Co-administration of Mobocertinib with multiple doses of Itraconazole or Ketoconazole (strong CYP3A inhibitors) is predicted to increase the steady-state combined molar AUC of Mobocertinib and its active metabolites by 374 to 419%.

Effect of CYP3A Inducers on Mobocertinib: Coadministration of Mobocertinib with multiple doses of rifampin (a strong CYP3A inducer) is predicted to decrease the steady-state combined molar AUC of Mobocertinib and its active metabolites by 92%.

Effect of Mobocertinib on CYP3A Substrates: Coadministration of Mobocertinib 160 mg once daily with oral or intravenous midazolam (a CYP3A substrate) decreased the AUC of midazolam by 32% and 16%, respectively.

Effect of Mobocertinib on BCRP Substrates: The clinical significance of changes in the pharmacokinetics of sulfasalazine (a BCRP substrate) when coadministered with multiple doses of Mobocertinib is unknown.

In Vitro Studies

CYP Enzymes: Mobocertinib, AP32960, and AP32914 do not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, or 2D6 at clinically relevant concentrations.

Transporter Systems: Mobocertinib is an inhibitor of P-gp and BCRP. At clinically relevant concentrations, Mobocertinib does not inhibit BSEP, MATE1, MATE2-K, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, or OCT2.

Mobocertinib is a substrate of P-gp. Mobocertinib is not a substrate of BCRP, OATP1B1, and OATP1B3.

INDICATIONS AND USAGE

Mobocertinib is a kinase inhibitor indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

DOSAGE AND ADMINISTRATION

Patient Selection

Select patients with locally advanced or metastatic NSCLC for treatment with Mobocertinib based on the presence of EGFR exon 20 insertion mutations.

Recommended Dosage

The recommended dosage of Mobocertinib is 160 mg orally once daily until disease progression or unacceptable toxicity.

Take Mobocertinib with or without food, at the same time each day. Swallow Mobocertinib capsules whole. Do not open, chew or dissolve the contents of the capsules.

If a dose is missed by more than 6 hours, skip the dose and take the next dose the following day at its regularly scheduled time.

If a dose is vomited, do not take an additional dose. Take the next dose as prescribed the following day.

Dosage Modifications for Adverse Reactions

Mobocertinib dose reduction levels for adverse reactions are summarized in Table 1.

Dose Reductions	Dose Level
First dose reduction	120 mg once daily
Second dose reduction	80 mg once daily

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

QTc Prolongation and Torsades de Pointes

Mobocertinib can cause life-threatening heart rate-corrected QT (QTc) prolongation, including Torsades de Pointes, which can be fatal.

Interstitial Lung Disease (ILD)/Pneumonitis

Mobocertinib can cause ILD/pneumonitis, which can be fatal.

Cardiac Toxicity

Mobocertinib can cause cardiac toxicity (including decreased ejection fraction, cardiomyopathy, and congestive heart failure) resulting in heart failure which can be fatal.

Diarrhea

Mobocertinib can cause diarrhea, which can be severe.

Embryo-Fetal Toxicity

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

SIDE EFFECTS

The most common side effects of Mobocertinib include:

- Diarrhea
- Rash
- Nausea, Vomiting
- Mouth sores
- Decrease appetite
- Infection of skin around nails
- Tiredness
- Dry skin
- Muscle or bone pain

DRUG INTERACTIONS

CYP3A Inhibitors

Avoid concomitant use of Mobocertinib with strong or moderate CYP3A inhibitors. If concomitant use of a moderate CYP3A inhibitor is unavoidable, reduce the dose of Mobocertinib.

CYP3A Inducers

Avoid concomitant use of Mobocertinib with strong or moderate CYP3A inducers.

USE IN SPECIFIC POPULATIONS

Pregnancy

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

Lactation

There are no data on the presence of Mobocertinib or its metabolites in human milk or their effects on the breastfed child or on milk production.

Females and Males of Reproductive Potential

Mobocertinib can cause fetal harm when administered to pregnant women.

Pediatric Use

The safety and effectiveness of Mobocertinib in pediatric patients have not been established.

Geriatric Use

No overall difference in effectiveness was observed between patients aged 65 and older and younger patients.

Renal Impairment

No dosage adjustment of Mobocertinib is recommended for patients with mild to moderate renal impairment.

Hepatic Impairment

The recommended dosage of Mobocertinib has not been established for patients with severe hepatic impairment.

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

Moboxen capsule: Each HDPE container contains 60 capsules (each capsule contains 40 mg Mobocertinib) 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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