Osimert

Osimertinib 80 mg

Everest

COMPOSITION

Osimert Tablet: Each film coated tablet contains Osimertinib mesylate INN 95.4 mg equivalent to Osimertinib 80 mg.

INDICATIONS AND USAGE

Osimertinib (**Osimert**) is a kinase inhibitor indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy.

DOSAGE AND ADMINISTRATION

Recommended Dosage Regimen

The recommended dose of Osimertinib (**Osimert**) is 80 mg tablet once a day until disease progression or unacceptable toxicity. Osimertinib (**Osimert**) can be taken with or without food. If a dose of Osimertinib (**Osimert**) is missed, do not make up the missed dose and take the next dose as scheduled.

Administration to Patients Who Have Difficulty in Swallowing Solids

Disperse tablet in 4 tablespoons (approximately 50 mL) of non-carbonated water only. Stir until tablet is completely dispersed and swallow or administer through naso-gastric tube immediately. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 4 to 8 ounces of water and immediately drink or administer through the naso-gastric tube.

Dose Modification for Adverse Reactions

Table: Recommended Dose Modifications for Osimertinib (**Osimert**).

Target Organ	Adverse Reaction	Dose Modification
Pulmonary	Interstitial lung disease (ILD)/Pneumonitis	Permanently discontinue Osimertinib (**Osimert**).
Cardiac	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold Osimertinib (**Osimert**) until QTc interval is less than 481 msec or recovery to baseline. If baseline QTc is greater than or equal to 481 msec, then resume at 40 mg dose.
	QTc interval prolongation with signs/ symptoms of life-threatening arrhythmia	Permanently discontinue Osimertinib (**Osimert**).
	Asymptomatic, absolute decrease in LVEF of 10% from baseline and below 50%	Withhold Osimertinib (**Osimert**) for up to 4 weeks. • If improved to baseline LVEF, resume. • If not improved to baseline, permanently discontinue.
	Symptomatic congestive heart failure	Permanently discontinue Osimertinib (**Osimert**).
Other	Adverse reaction of Grade 3 or greater severity	Withhold Osimertinib (**Osimert**) for up to 3 weeks.
	If improvement to Grade 0-2 within 3 weeks	Resume at 80 mg or 40 mg daily.
	If no improvement within 3 weeks	Permanently discontinue Osimertinib (**Osimert**).

ECGs = Electrocardiograms
LVEF = Left Ventricular Ejection Fraction
QTc = QT interval corrected for heart rate

CONTRAINDICATIONS

Hypersensitivity to Osimertinib or to any of the additives.

WARNINGS AND PRECAUTIONS

Interstitial Lung Disease (ILD)/ Pneumonitis

Interstitial Lung Disease (ILD)/Pneumonitis occurred in 3.3% of patients. Permanently discontinue Osimertinib (**Osimert**) in patients diagnosed with ILD/Pneumonitis.

QTc Interval Prolongation

Monitor electrocardiograms and electrolytes in patients who have a history or predisposition for QTc prolongation, or those who are taking medications that are known to prolong the QTc interval. Withhold then restart at a reduced dose or permanently discontinue Osimertinib (**Osimert**).

Cardiomyopathy

Cardiomyopathy occurred in 1.4% of patients. Assess left ventricular ejection fraction (LVEF) before treatment and then every 3 months thereafter.

Keratitis

Advise patients to contact their healthcare provider immediately if they develop eye symptoms (eye inflammation, lacrimation, light sensitivity, eye pain, red eye or changes in vision)

Embryo-Fetal Toxicity

Osimertinib (**Osimert**) can cause fetal harm. Advise females of potential risk to the fetus and to use effective contraception during treatment with Osimertinib (**Osimert**) and for 6 weeks after final dose. Advise males to use effective contraception for 4 months, after the last dose of Osimertinib (**Osimert**).

ADVERSE REACTIONS

Most common adverse reactions (≥ 25%) were diarrhea, rash, dry skin and nail toxicity.

DRUG INTERACTIONS

Effect of Other Drugs on Osimertinib

Strong CYP3A Inhibitors

Avoid concomitant administration of Osimertinib (**Osimert**) with strong CYP3A inhibitors, including macrolide antibiotics (e.g., Telithromycin), antifungals (e.g., Itraconazole), antivirals (e.g., Ritonavir), Nefazodone, as concomitant use of strong CYP3A inhibitors may increase Osimertinib (**Osimert**) plasma concentrations. If no other alternative exists, monitor patients more closely for adverse reactions of Osimertinib (**Osimert**).

Strong CYP3A Inducers

Avoid concomitant administration of Osimertinib (**Osimert**) with strong CYP3A inducers (e.g., Phenytoin, Rifampicin, Carbamazepine, St. John's Wort) as strong CYP3A inducers may decrease Osimertinib (**Osimert**) plasma concentrations.

Effect of Osimertinib on Other Drugs

Avoid concomitant administration of Osimertinib (**Osimert**) with drugs that are sensitive substrates of CYP3A, breast cancer resistance protein (BCRP), or CYP1A2 with narrow therapeutic indices, including but not limited to Fentanyl, Cyclosporine, Quinidine, Ergot Alkaloids, Phenytoin, Carbamazepine, as Osimertinib (**Osimert**) may increase or decrease plasma concentrations of these drugs.

USE IN SPECIFIC POPULATIONS

Pregnancy

Osimertinib (**Osimert**) can cause fetal harm when administered to a pregnant woman. There is no available data on Osimertinib (**Osimert**) use in pregnant women.

Lactation

There is no data on the presence of Osimertinib (**Osimert**) in human milk, the effects of Osimertinib (**Osimert**) on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in breastfed infants from Osimertinib (**Osimert**), advise a lactating woman not to breastfeed during treatment with Osimertinib (**Osimert**) and for 2 weeks after the final dose.

Females and Males of Reproductive Potential

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with Osimertinib (**Osimert**) and for 6 weeks after the final dose.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during and for 4 months following the final dose of Osimertinib (**Osimert**).

Infertility

Based on animal studies, Osimertinib (**Osimert**) may impair fertility in females and males of reproductive potential. It is not known if the effects on fertility are reversible.

Pediatric Use

The safety and effectiveness of Osimertinib (**Osimert**) in pediatric patients have not been established.

Geriatric Use

No overall differences in effectiveness were observed based on age. Exploratory analysis suggest a higher incidence of Grade 3 and 4 adverse reactions (32% versus 25%) and more frequent dose modifications for adverse reactions (23% versus 17%) in patients 65 years or older as compared to those younger than 65 years.

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Renal Impairment

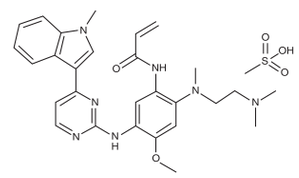
No dedicated clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of Osimertinib. Based on population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild [creatinine clearance (CLcr) 60-89 mL/min] or moderate (CLcr 30-59 mL/min) renal impairment. There is no recommended dose of Osimertinib (**Osimert**) for patients with severe renal impairment (CLcr<30 mL/min) or end-stage-renal disease.

Hepatic Impairment

No dedicated clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of Osimertinib. Based on population pharmacokinetic (PK) analysis, no dose adjustment is recommended in patients with mild hepatic impairment [total bilirubin <upper limit of normal (ULN) and AST between 1 to 1.5 times ULN or total bilirubin between 1.0 to 1.5 times ULN and any AST]. There is no recommended dose for Osimertinib (**Osimert**) for patients with moderate or severe hepatic impairment.

DESCRIPTION

Osimertinib is a kinase inhibitor for oral administration. The molecular formula for Osimertinib mesylate is $C_{28}H_{33}N_7O_2 \bullet CH_4O_3S$, and the molecular weight is 596 g/mol. The chemical name is N-(2-{2-dimethylaminoethyl-methylamino}-4-methoxy-5-{[4-(1-methylindol-3-yl)pyrimidin-2-yl]amino}phenyl)prop-2-enamide mesylate salt. Osimertinib has the following structural formula (as osimertinib mesylate):



Osimert tablets contain 80 mg of Osimertinib, equivalent to 95.4 mg of Osimertinib mesylate. Required pharmaceuticals additives were added to ensure the best tablet dosage form.

CLINICAL PHARMACOLOGY

Mechanism of Action

Osimertinib is kinase inhibitor of the epidermal growth factor receptor (EGFR), which binds irreversibly to certain mutant forms of EGFR (T790M, L858R, and exon 19 deletion) at approximately 9-fold lower concentrations than wild-type. In cultured cells and animal tumor implantation models, Osimertinib exhibited anti-tumor activity against NSCLC lines harboring EGFR-mutations (T790M/L858R, L858R, T790M/exon 19 deletion, and exon 19 deletion) and, to a lesser extent, wild-type EGFR amplifications. Two pharmacologically active metabolites (AZ7550 and AZ5104 circulating at approximately 10% of the parent) with similar inhibitory profiles to Osimertinib have been identified in the plasma after oral administration of Osimertinib. AZ7550 showed a similar potency to Osimertinib, while AZ5104 showed greater potency against exon 19 deletion and T790M mutants (approximately 8-fold) and wild- type (approximately 15-fold) EGFR. *In vitro*, Osimertinib also inhibited the activity of HER2, HER3, HER4, ACK1, and BLK at clinically relevant concentrations.

Pharmacokinetics

The area under the plasma concentration-time curve (AUC) and maximal plasma concentration (Cmax) of Osimertinib increased dose proportionally over 20 to 240 mg dose range (i.e., 0.25 to 3 times the recommended dosage) after oral administration and exhibited linear pharmacokinetics (PK). Administration of Osimertinib orally once daily resulted in approximately 3-fold accumulation with steady state exposures achieved after 15 days of dosing. At steady state, the Cmax to Cmin (minimal concentration) ratio was 1.6-fold.

Absorption

The median time to Cmax of Osimertinib was 6 hours (range 3-24 hours). Following administration of a 20 mg Osimertinib tablets with a high-fat, high-calorie meal (containing approximately 58 grams of fat and 1000 calories), the Cmax and AUC of Osimertinib increased by 14% and 19% respectively, compared to fasting conditions.

Distribution

The mean volume of distribution at steady-state (V_{ss}/F) of Osimertinib was 986L. Plasma protein binding of Osimertinib is likely high based on its physiochemical properties.

Elimination

Osimertinib plasma concentrations decreased with time and a population estimated mean half-life of Osimertinib was 48 hours, and oral clearance (CL/F) was 14.2 (L/h).

Metabolism

The main metabolic pathways of Osimertinib were oxidation (predominantly CYP3A) and dealkylation *in vitro*. Two pharmacologically active metabolites (AZ7550 and AZ5104) have been identified in the plasma after Osimertinib oral administration. The geometric mean exposure (AUC) of each metabolite (AZ5104 and AZ7550) was approximately 10% of the exposure of Osimertinib at steady-state.

Excretion

Osimertinib is primarily eliminated in the feces (68%) and to a lesser extent in the urine (14%). Unchanged Osimertinib accounted for approximately 2% of the elimination.

Specific Populations

No clinically significant differences in the pharmacokinetics of Osimertinib were observed based on age, sex, ethnicity, body weight, smoking status, mild (CLcr 60-89 mL/min) or moderate (CLcr 30-59 mL/min) renal impairment, or mild hepatic impairment (total bilirubin <ULN and AST between 1 to 1.5x ULN or total bilirubin between 1.0 to 1.5 times ULN and any AST). There are no data on the pharmacokinetics of Osimertinib in patients with severe renal impairment (CLcr less than 30 mL/min) or with moderate to severe hepatic impairment (moderate: total bilirubin between 1.5 to 3.0 times ULN and any AST, and severe: total bilirubin between 3.0-10 times ULN and any AST).

Drug Interactions

Clinical studies evaluating Osimertinib in the presence of strong CYP3A inhibitors have not been conducted. Clinical studies evaluating Osimertinib in the presence of strong CYP3A inducers have not been conducted. The exposure of Osimertinib was not affected by concurrent administration of a single 80 mg Osimertinib tablet following 40 mg omeprazole administration for 5 days.

Osimertinib is a competitive inhibitor of CYP3A, but not CYP2C8, 1A2, 2A6, 2B6, 2C9, 2C19, 2D6 and 2E1 *in vitro*. Osimertinib induced CYP3A4 (Pregnane X dependent) and CYP1A2 enzymes.

Based on *in vitro* studies, osimertinib is a substrate of P-glycoprotein and BCRP and is not a substrate of OATP1B1 and OATP1B3. Osimertinib is an inhibitor of BCRP and does not inhibit P-glycoprotein, OAT1, OAT3, OATP1B1, OATP1B3, MATE1, MATE2K and OCT2 *in vitro*.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with Osimertinib. Osimertinib did not cause genetic damage in *in vitro and in vivo* assays.

Based on studies in animals, male fertility may be impaired by treatment with Osimertinib. Degenerative changes were present in the testes in rats and dogs exposed to Osimertinib for 1 month or more with evidence of reversibility in the rat. Following administration of Osimertinib to rats for approximately 10 weeks at a dose of 40 mg/kg, at exposures 0.5-times the AUC observed in patients at the recommended dose of 80 mg, there was a reduction in male fertility, demonstrated by increased pre-implantation loss in untreated females mated to treated males.

Nonclinical female fertility studies have not been conducted. In repeat dose toxicity studies, histological evidence of anestrus, corpora lutea degeneration in the ovaries and epithelial thinning in the uterus and vagina were seen in rats exposed to Osimertinib for 1 month or more at exposures 0.3-times the AUC observed in patients at the recommended dose of 80 mg. Findings in the ovaries seen following 1 month of dosing exhibited evidence of reversibility.

PHARMACEUTICAL INFORMATION

Storage Conditions

Store in a cool and dry place. Do not store above 30°C.

Keep **Osimert** out of the reach and sight of children.

HOW SUPPLIED

Osimert Tablet: Each HDPE container contains 30 tablets each of which contains Osimertinib mesylate INN 95.4 mg equivalent to Osimertinib 80 mg.

Manufactured By

Everest Pharmaceuticals Ltd.

Narayangonj, Bangladesh

www.everestpharmabd.com