

Tagrix

Osimertinib

COMPOSITION:

Tagrix 40 Tablet: Each film coated tablet contains Osimertinib Mesylate INN equivalent to Osimertinib 40 mg.

Tagrix 80 Tablet: Each film coated tablet contains Osimertinib Mesylate INN equivalent to Osimertinib 80 mg.

CLINICAL PHARMACOLOGY:

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 (C_{max}) 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 C_{max} to C_{min} (minimal concentration) ratio was 1.6-fold.

Absorption

The median time to C_{max} 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 C_{max} 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 986 L. Plasma protein binding of Osimertinib is likely high based on its physicochemical 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).

INDICATION:

Osimertinib 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:

Standard Dosage

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

Administration to patients who have difficulty in swallowing: 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

Target Organ	Adverse Reaction ^a	Dose Modification
Pulmonary	Interstitial lung disease (ILD)/Pneumonitis	Permanently discontinue Osimertinib.
Cardiac	QTc ⁱ interval greater than 500 msec on at least 2 separate ECGs ^b	Withhold Osimertinib 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.
	Asymptomatic, absolute decrease in LVEF ^c of 10% from baseline and below 50%	Withhold Osimertinib 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.
Other	Grade 3 or higher adverse reaction	Withhold Osimertinib 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.

^a Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0).

^b ECGs = Electrocardiograms ^c LVEF = Left Ventricular Ejection Fraction ⁱ QTc = QT interval corrected for heart rate

USE IN SPECIAL POPULATION:

Pregnancy

Osimertinib can cause fetal harm when administered to a pregnant woman. There are no available data on Osimertinib use in pregnant women.

Lactation

There are no data on the presence of Osimertinib in human milk, the effects of Osimertinib on the breastfed infant or on milk production.

Contraception

Females: Advise females of reproductive potential to use effective contraception during treatment with Osimertinib 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.

Infertility

Based on animal studies, Osimertinib 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 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.

Renal impairment

There is no recommended dose of Osimertinib for patients with severe renal impairment (CLcr < 30 mL/min) or end-stage-renal disease.

Hepatic Impairment

There is no recommended dose for Osimertinib for patients with moderate or severe hepatic impairment.

CONTRAINDICATION:

None

PRECAUTION:

Interstitial Lung Disease (ILD)/Pneumonitis

Occurred in 3.3% of patients. Permanently discontinue Osimertinib 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.

Cardiomyopathy

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

Embryo-Fetal Toxicity

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

ADVERSE REACTION:

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

DRUG INTERACTION:

Strong CYP3A Inhibitors

Avoid concomitant administration of Osimertinib 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 plasma concentrations. If no other alternative exists, monitor patients more closely for adverse reactions of Osimertinib.

Strong CYP3A Inducers

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

Effect on other drugs

Avoid concomitant administration of Osimertinib 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 may increase or decrease plasma concentrations of these drugs.

PHARMACEUTICAL INFORMATION:

Storage Conditions

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

Presentation & Packaging

Tagrix 40 Tablet: Each commercial box contains 30 tablets in Alu-Alu blister pack.

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Manufactured By

 Beacon
 Pharmaceuticals Limited
 Mymensingh, Bangladesh

Only for Export