TASSO

Osimertinib

Julphar Bangladesh | جلفار بنغلاديش

COMPOSITION:

TASSO 40 Tablet: Each film coated tablet contains Osimertinib Mesylate INN equivalent to Osimertinib 40 mg.
TASSO 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 (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 withsteady 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 were compared to that under fasting conditions.

Distribution

The mean volume of distribution at steady-state (Vss/F) of Osimertinib was 986 L. Plasma protein binding of Osimertinib was 95%.

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, baseline albumin, line of therapy, smoking status, mild (CLcr 60-89 ml/min), moderate (CLcr 30-59 ml/min, as estimated by C-G), or severe (CLcr 15-29 ml/min) renal impairment, or mild (total bilirubin ≤ ULN and AST > ULN or total bilirubin between 1 to 1.5 times ULN and any AST) or moderate (total bilirubin between 1.5 to 3 times ULN and any AST) hepatic impairment. The pharmacokinetics of osimertinib in patients with end-stage renal disease (CLcr < 15 ml/min) or with severe hepatic impairment (total bilirubin between 3 to 10 times ULN and any AST) are unknown.

INDICATION:

TASSO is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.
TASSO is indicated for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

DOSAGE AND ADMINISTRATION:

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.
Disperse tablet in 60 ml (2 ounces) of non-carbonated water only. Stir until tablet is dispersed into small pieces (the tablet will not completely dissolve) and swallow immediately. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 120 ml to 240 ml (4 to 8 ounces) of water and immediately drink.
If administration via nasogastric tube is required, disperse the tablet as above in 15 ml of non-carbonated water, and then use an additional 15 ml of water to transfer any residues to the syringe. The resulting 30 ml liquid should be administered as per the nasogastric tube instructions with appropriate water flushes (approximately 30 ml).

Dose Modification

Target Organ	Adverse Reaction[a]	Dose Modification
Pulmonary	Interstitial lung disease (ILD) / Pneumonitis	Permanently discontinue Osimertinib.
Cardiac	QTc[†] 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.
	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 Eventsversion 4.0 (NCI CTCAE v4.0).

[b]ECGs = Electrocardiograms

[†]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. The effects on female fertility showed a trend toward reversibility. It is not known whether the effects on male 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 (13.4% versus 9.3%) and more frequent dose modifications for adverse reactions (13.4% versus 7.6%) in patients 65 years or older as compared to those younger than 65 years.

Renal impairment

No dose adjustment is recommended in patients with mild, [creatinine clearance (CLcr) 60-89 ml/min, as estimated by the Cockcroft Gault method (C-G)], moderate, (CLcr 30-59 ml/min) or severe (CLcr 15- 29 ml/min) renal impairment. There is no recommended dose of Osimertinib for patients with end-stage renal disease.

Hepatic Impairment

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

CONTRAINDICATION:

None

WARNINGS AND PRECAUTION:

Interstitial Lung Disease (ILD)/Pneumonitis

Interstitial lung disease (ILD)/pneumonitis occurred in 3.9% of the 1142 Osimertinib-treated patients; 0.4% of cases were fatal.

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 (≥20%) were diarrhea, rash, dry skin, nail toxicity, stomatitis, fatigue and decreased appetite.

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 below 30^0 C, protect from light. Keep out of the reach of children.

How supplied

TASSO 40 Tablet: Each box contains 30 tablets and one packet silica gel in a sealed plastic container.

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Manufactured by:
Julphar Bangladesh Ltd.
Sreepur, Gazipur, Bangladesh.