Osemax

Osimertinib Tablet

COMPOSITION
Osemax Tablet: Each film coated tablet contains Osimertinib Mesylate equivalent to Osimertinib 80 mg.

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-muta-tions (T790M/L858R, L858R, T790M/exon 19 deletion, and exon 19 deletion) and, to a lesser extent, wild-type EGFR amplifica-tions. 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 approxi-mately 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/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 pharma-cologically 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).

INDICATIONS AND USAGE
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
Recommended Dosage Regimen: 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 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:

Recommended Dose Modifications for Osimertinib:

Target Organ	Adverse Reaction	Dose Modification
Pulmonary	Interstitial lung disease (ILD)/Pneumonitis	Permanently discontinue Osimertinib
Cardiac	QTc interval greater than 500 msec on at least 2 separate ECGs	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 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	Adverse reaction of Grade 3 or greater severity	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.

ECGs : Electrocardiograms
LVEF : Left Ventricular Ejection Fraction
QTcQT : 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 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
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 can cause fetal harm. Advise females of potential risk to the fetus and to use effective contraception during treatment with Osimertinib (Osemax) and for 6 weeks after final dose. Advise males to use effective contraception for 4 months, after the last dose of Osimertinib.

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 (Osemax) 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 (Osemax) plasma concen-trations. If no other alternative exists, monitor patients more closely for adverse reactions of Osimertinib.
Strong CYP3A Inducers
Avoid concomitant administration of Osimertinib (Osemax) with strong CYP3A inducers (e.g., Phenytoin, Rifampicin, Carbamaz-epine, St. John's Wort) as strong CYP3A inducers may decrease Osimertinib (Osemax) plasma concentrations.
Effect of Osimertinib on Other Drugs
Avoid concomitant administration of Osimertinib (Osemax) 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 (Osemax) may increase or decrease plasma concentrations of these drugs.

USE IN SPECIFIC POPULATIONS
Pregnancy
Osimertinib (Osemax) can cause fetal harm when administered to a pregnant woman. There is no available data on Osimertinib (Osemax) use in pregnant women.
Lactation
There is no data on the presence of Osimertinib (Osemax) in human milk, the effects of Osimertinib (Osemax) on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in breastfed infants from Osimerti-nib advise a lactating woman not to breastfeed during treatment with Osimertinib (Osemax) 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 (Osemax) 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 (Osemax) 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 (Osemax) 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: 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 (Osemax) 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 (Osemax) for patients with moderate or severe hepatic impairment.

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, 2019, 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-glyco-protein 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 adminis-tration 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-implan-tation 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.

STORAGE
Store below 30°C. Protected from light & moisture. Keep all medicines out of the reach of children.

PACKAGING
Osemax Tablet: Each child-resistant HDPE container contains 30 tablets and one packet silica gel.

Apex™ Pharma

Manufactured by
Apex Pharma Limited
Shafipur, Kaliakair, Gazipur, Bangladesh