# Irmukin

Osimertinib INN Tablet

**"Please carefully read the full leaflet"**

## COMPOSITION

**Irmukin** (Osimertinib) 40 mg tablet: Each Film coated tablet contains Osimertinib Mesylate INN equivalent to Osimertinib 40 mg.

**Irmukin** (Osimertinb) 80 mg tablet: Each Film coated tablet contains Osimertinib Mesylate INN equivalent to Osimertinib 80 mg.

## PHARMACEUTICAL FORM AND STRENGTH

**Irmukin** (Osimertinib) is available as 40 mg and 80 mg film coated tablet for oral administration.

## 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 dimethylaminoeth-yl-methylamino}-4-methoxy-5-{[4-(1-methylindol-3-yl)pyrimidin-2yl]amino}phenyl)prop-2-enamide mesylate salt.

## THERAPEUTIC INDICATIONS

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 tyrosine kinase inhibitor therapy.

## DOSAGE AND ADMINISTRATION

Recommended dose is 80 mg orally once daily, with or without food.

## 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. |
| | Asymptomatic, absolute decrease in LVEF[c] of 10% from baseline and below 50% | Withhold Osimertinib for up to 4 weeks.<br>• If improved to baseline LVEF, resume.<br>• If not improved to baseline, permanently discontinue. |
| | Symptomatic congestive heart failure | Permanently discontinue Osimertinib. |
| Others | 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
[†]QTc = QT interval corrected for heart rate

## 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 non-small cell lung cancer (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.

## PHARMACOKINETICS

**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 (Vss/F) of Osimertinib was 986 L. 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.

## CONTRAINDICATION

None.

## USE IN SPECIFIC POPULATION

### Pregnancy

Based on its mechanism of action and animal data, Osimertinib can cause fetal harm when administered to a pregnant woman. There are no available data on Osimertinib use in pregnant women. Pregnant women should be advised of the potential risk to a fetus.
There are no data on the presence of Osimertinib in human milk, the effects of Osimertinib on the breastfed infant or on milk production. Lactating woman should be advised not to breastfeed during treatment.

### Pediatric Use

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

### Geriatric Use

No overall differences in safety were observed between patients 65 years and older and those younger than 65 years.

## WARNINGS AND PRECAUTIONS

- Interstitial lung disease (ILD): Occurred in 3.3% of patients. Should be Withheld Osimertinib with any patient who presents with worsening of respiratory symptoms. Need discontinue Osimertinib if ILD is confirmed.
- QTc Interval Prolongation: Electrocardiograms and electrolytes should be monitored 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. Osimertinib should be withheld then restarted at a reduced dose or permanently discontinued.
- Cardiomyopathy: Occurred in 1.4% of patients. Left ventricular ejection fraction (LVEF) should be assessed before treatment and then every 3 months thereafter. Withhold treatment with Osimertinib if ejection fraction decreased by 10% from pretreatment values and is less than 50%. For symptomatic congestive heart failure or persistent, asymptomatic LV dysfunction that does not resolve within 4 weeks, permanently discontinue Osimertinib.
- Embryo-Fetal Toxicity: Osimertinib can cause fetal harm. Females should be advised of potential risk to the fetus and to use effective contraception during treatment with Osimertinib and for 6 weeks after final dose. Males should be advised to use effective contraception for 4 months, after the last dose of Osimertinib.

## ADVERSE REACTIONS

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

## DRUG INTERACTIONS

### Drug interactions

### Strong CYP3A Inhibitors

Concomitant administration of Osimertinib should be avoided with strong CYP3A inhibitors, including macrolide antibiotics (e.g., telithromycin), antifungals (e.g., litraconazole), antivirals (e.g., ritonavir), nefazodone, as concomitant use of strong CYP3A inhibitors may increase Osimertinib plasma concentrations. If no other alternative exists, patients should be monitored more closely for adverse reactions.

### Strong CYP3A Inducers

Concomitant administration of Osimertinib should be avoided with strong CYP3A inducers (e.g., phenytoin, rifampicin, carbamazepine, St. John's Wort) as strong CYP3A inducers may decrease Osimertinib plasma concentrations.

## PHARMACEUTICAL INFORMATIONS

### Storage Conditions

Store below $30^0$ C.
Store in cool and dry place.
Keep away from light.
Keep out of the reach of children.

## HOW SUPPLIED

**Irmukin 40 mg Tablets:** Each commercial box contains 3x10's tablets in Alu-Alu blister pack.
**Irmukin 40 mg Tablets:** Each commercial box contains 6x10's tablets in Alu-Alu blister pack.
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## MANUFACTURED BY

genvio

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