Getinib
Tablet

Composition: Getinib: Each film coated tablet contains Gefitinib INN 250 mg.

Clinical Pharmacology: Gefitinib reversibly inhibits the kinase activity of wild-type and certain activating mutations of EGFR, preventing autophosphorylation of tyrosine residues associated with the receptor, thereby inhibiting further downstream signalling and blocking EGFR-dependent proliferation. Gefitinib binding affinity for EGFR exon 19 deletion or exon 21 point mutation L858R mutations is higher than its affinity for the wild-type EGFR. It also inhibits IGF and PDGF-mediated signalling at clinically relevant concentrations; inhibition of other tyrosine kinase receptors has not been fully characterized.

Pharmacokinetics:

Absorption and Distribution: The mean oral bioavailability is 60%, with peak plasma levels occurring 3-7 hours after dosing. Food does not alter its bioavailability to a clinically meaningful extent. In vitro binding of Gefitinib to human plasma proteins (serum albumin and α1-acid glycoprotein) is 90%, independent of drug concentrations.

Metabolism and Elimination: Gefitinib undergoes extensive hepatic metabolism in humans, predominantly by CYP3A4. Three sites of biotransformation have been identified: metabolism of the N-propoxymorpholino-group, demethylation of the methoxysubstituent on the quinazoline, and oxidative defluorination of the halogenated phenyl group. Five metabolites have been fully identified in fecal extracts and the major active component was O-desmethyl Gefitinib produced by CYP2D6 metabolism and accounted for 14% of the dose.

Gefitinib is cleared primarily by the liver, with total plasma clearance and elimination half-life of 48 hours after intravenous administration. Steady state plasma concentrations are achieved within 10 days after daily dosing. Excretion of it and its metabolites is predominantly via the feces (86%), with renal elimination accounting for less than 4% of the administered dose.

Indications: Getinib 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) substitution mutations as detected by an FDA-approved test.

Dosage and Administration: The recommended dose of Getinib is 250 mg orally once daily with or without food until disease progression or unacceptable toxicity. One should not take a missed dose within 12 hours of the next dose.

Administration to Patients who have Difficulty Swallowing Solids: Getinib tablets should be immersed in 4 to 8 ounces of water by dropping the tablet in water, and stirred for approximately 15 minutes. The liquid should be immediately drunk or administered through a naso-gastric tube. The container should be rinsed with 4 to 8 ounces of water and immediately drunk or administered through the naso- gastric tube.

Dose Modification: Getinib should be withheld (for up to 14 days) for any of the following:

- Acute onset or worsening of pulmonary symptoms (dyspnea, cough, fever).
- NCI CTCAE Grade 2 or higher in ALT and/or AST elevations.
- NCI CTCAE Grade 3 or higher diarrhea.
- Signs and symptoms of severe or worsening ocular disorders including keratitis.
- NCI CTCAE Grade 3 or higher skin reactions.

Treatment with Getinib should be resumed when the adverse reaction fully resolves or improves to NCI CTCAE Grade1.

Getinib should be permanently discontinued for:

- Confirmed interstitial lung disease (ILD).
- Severe hepatic impairment.
- Gastrointestinal perforation.
- Persistent ulcerative keratitis.

Or, as directed by the registered physician.

Side Effects: The most common side effects of this tablet are- Interstitial Lung Disease, Hepatotoxicity, Gastrointestinal Perforation, Severe or Persistent Diarrhea, Ocular Disorders including Keratitis, Bullous and Exfoliative Skin Disorders.

Contraindications: It is contraindicated in patients with known hypersensitivity to Gefitinib or any other components of this drug.

Use in pregnancy and lactation: There are no adequate and well-controlled studies in pregnant women using Gefitinib. If it is used during pregnancy or if the patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

Lactation: It is not known whether Getinib is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Getinib, women should be advised to discontinue breast-feeding during treatment with Getinib.

Pediatric Use: The safety and effectiveness of Getinib in pediatric patients have not been established.

Renal Impairment : No clinical studies were conducted with Getinib in patients with severe renal impairment.

Hepatic Impairment: Adverse reactions should be monitored when Getinib is administered to patients with moderate and severe hepatic impairment.

Drug Interactions:

Drugs affecting Gefitinib Exposure: CYP3A4 Inducer: Drugs that are strong inducers of CYP3A4 increase the metabolism of Gefitinib and decrease Gefitinib plasma concentrations. Getinib should be increased to 500 mg daily in patients receiving a strong **CYP3A4** inducer (e.g., rifampicin, phenytoin, or tricyclic antidepressant) and should be resumed at 250 mg 7 days after discontinuation of the strong inducer. **CYP3A4 Inhibitor:** Drugs that are strong inhibitors of **CYP3A4** (e.g., ketoconazole and itraconazole) decrease Gefitinib metabolism and increase Gefitinib plasma concentrations.

Precautions:

Intestinal lung disease (ILD): ILD or ILD-like adverse drug reactions (e.g., lung infiltration, pneumonitis, acute respiratory distress syndrome, or pulmonary fibrosis) occurred in 1.3% of the 2462 patients who received Getinib across clinical trials. Getinib should be withheld and promptly investigated for ILD in any patient who presents with worsening of respiratory symptoms such as dyspnea, cough and fever. It should be permanently discontinued if ILD is confirmed.

Hepatotoxicity: Patients receiving Getinib across clinical trials, 11.4% of patients had increased alanine aminotransferase (ALT), 7.9% of patients had increased aspartate aminotransferase (AST), and 2.7% of patients had increased bilirubin. Periodic liver function testing should be obtained. Getinib should be withheld in patients with worsening liver function and discontinued in patients with severe hepatic impairment.

Gastrointestinal Perforation: Gastrointestinal perforation occurred in three (0.1%) of the 2462 Getinib-treated patients across clinical trials. It should be permanently discontinued in patients who develop gastrointestinal perforation.

Severe or Persistent Diarrhea: Grade 3 or 4 diarrhea occurred in 3% of 2462 Getinib-treated patients across clinical trials. It should be withheld for severe or persistent (up to 14 days) diarrhea.

Ocular Disorders including Keratitis: Ocular disorders [keratitis (0.1%), corneal erosion and aberrant eyelash growth (0.2%), conjunctivitis, blephritis and dry eye (6.7%)] occurred in the 2462 Getinib-treated patients across clinical trials. It should be interrupted or discontinued for severe, or worsening ocular disorders.

Bullous and Exfoliative Skin Disorders: Bullous conditions including toxic epidermal necrolysis, Stevens Johnson syndrome and erythema multiforme have been reported from treatment with Getinib. Erythema multiforme and dermatitis bullous have been reported in two patients (0.08%) across NSCLC trials. Getinib treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions.

Overdose: There are no specific measures/treatments that should be taken following Getinib overdosing.

Storage: Store at 20°- 25°C in a cool and dry place, away from sunlight. Keep out of the reach of children.

Packing: Each box contains 4x7's tablets in Alu- Alu blister pack.