DRUG INTERACTIONS

- In vitro studies have shown that the metabolism of gefitinib is predominantly via CYP3A4.
- Co-administration with rifampicin (a known potent CYP3A4 inducer) in healthy volunteers reduced mean gefitinib AUC by 83% of that without rifampicin.
- Co-administration with itraconazole (a CYP3A4 inhibitor) resulted in an 80% increase in the mean AUC of gefitinib.
- Co-administration of drugs that cause significant sustained elevations in gastric pH, ≥5, resulted in a reduced mean gefitinib AUC by 47%
- INR elevations and/or bleeding events have been reported in some patients taking warfarin

OVERDOSAGE

There is no specific treatment in the event of overdose of GEFITINIB. Adverse reactions associated with overdose should be treated symptomatically; in particular severe diarrhoea should be managed as clinically indicated.

DIRECTIONS

Store below 30°C. Protect from direct light. To be sold on prescription only. Keep out of the reach of children.

PRESENTATION

Gefitec 250 mg Tablets: 3 Strips of 10 Tablets each in a unit carton along with package insert.

جیفیٹک ۲۵۰ ملی گرام گولیاں

جیفٹنب

دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
دوا کو دھوپ اور نمی سے محفوظ رکھیں۔
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
بچوں کی پہنچ سے دور رکھیں۔

Marketed by:

Revive healthcare

503, 5th Floor, Eden Heights, 6 Main Gulberg, Jail Road, Lahore - Pakistan 54600.

Manufactured by:
United Biotech (P) Limited
Bagbania, Baddi-Nalagarh Road, Distt. Solan (HP) - 174 101 - India

℞ Gefitinib Tablets 250mg

GEFITEC 250 mg Tablets

PHARMACEUTICALS WORLDWIDE — UNITED BIOTECH — The Emergence of a New Standard

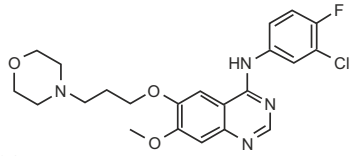
COMPOSITION

Each film coated tablet contains:
Gefitinib …….. 250 mg
(As per Innovator's specifications)

DESCRIPTION

Gefitinib is an anilinoquinazoline with the chemical name 4-Quinazolinamine, N-(3-chloro-4- fluorophenyl) -7-methoxy-6- [3-4-morpholin) propoxy]. It has the molecular formula $C_{22}H_{24}ClFN_4O_3$

Structural formula:



CLINICAL PHARMACOLOGY

Mechanism of Action

Gefitinib inhibits the intracellular phosphorylation of numerous tyrosine kinases associated with transmembrane cell surface receptors, including the tyrosine kinases associated with the epidermal growth factor receptor (EGFR-TK). EGFR is expressed on the cell surface of many normal cells and cancer cells.

Pharmacokinetics

Gefitinib is absorbed slowly after oral administration with mean bioavailability of 60%. Metabolism is primarily via CYP3A4 and excreted in feces. The elimination half-life is about 48 hours. Daily oral administration of gefitinib to cancer patients resulted in a 2-fold accumulation compared to single dose administration. Steady state plasma concentrations are achieved within 10 days.

Absorption and Distribution : Gefitinib is slowly absorbed, with peak plasma levels occurring 3-7 hours after dosing and mean oral bioavailability of 60%. Bioavailability is not significantly altered by food. Gefitinib is extensively distributed throughout the body with a mean steady state volume of distribution of 1400 L following intravenous administration. In vitro binding of gefitinib to human plasma proteins (serum albumin and α1-acid glycoprotein) is 90% and is 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 methoxy-substituent on the quinazoline and oxidative defluorination of the halogenated phenyl group.

Five metabolites were identified in human plasma. Only O-desmethyl gefitinib has exposure comparable to gefitinib. Although this metabolite has similar (epidermal growth factor receptor) EGFR-TK activity to gefitinib in the isolated enzyme assay, it had only 1/14 of the potency of gefitinib in one of the cell-based assays.

Gefitinib is cleared primarily by the liver, with total plasma clearance and elimination half-life values of 595 ml/min and 48 hours, respectively, after intravenous administration. Excretion is predominantly via the

feces (86%), with renal elimination of drug and metabolites accounting for less than 4% of the administered dose.

INDICATIONS

Gefitinib is indicated as monotherapy for the continued treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies who are benefiting or have benefited from gefitinib.

In light of positive survival data with other agents including another oral EGFR inhibitor, physicians should use other treatment options in advanced non-small cell lung cancer patient populations who have received one or two prior chemotherapy regimens and are refractory or intolerant to their most recent regimen.

DOSAGE & ADMINISTRATION

The recommended daily dose of gefitinib is one 250 mg tablet with or without food.

For Patients who have Difficulty Swallowing:

Gefitinib tablets can also be dispersed in half a glass of drinking water (non-carbonated). No other liquids should be used. Drop the tablet in the water, without crushing it, stir until the tablet is dispersed (approximately 10 minutes) and drink the liquid immediately. Rinse the glass with half a glass of water and drink. The liquid can also be administered through a naso-gastric tube.

Dosage Adjustment:

Patients with poorly tolerated diarrhea (sometimes associated with dehydration) or skin adverse drug reactions may be successfully managed by providing a brief (up to 14 days) therapy interruption followed by reinstatement of the 250 mg daily dose.

In the event of acute onset or worsening of pulmonary symptoms (dyspnea, cough, fever), gefitinib therapy should be interrupted and a prompt investigation of these symptoms should occur and appropriate treatment initiated. If interstitial lung disease is confirmed, gefitinib should be discontinued and the patient treated appropriately.

Patients who develop onset of new eye symptoms such as pain should be medically evaluated and managed appropriately, including gefitinib therapy interruption and removal of an aberrant eyelash if present. After symptoms and eye changes have resolved, the decision should be made concerning reinstatement of the 250 mg daily dose.

In patients receiving a potent CYP3A4 inducer such as rifampicin or phenytoin, a dose increase to 500 mg daily should be considered in the absence of severe adverse drug reaction, and clinical response and adverse events should be carefully monitored.

No dosage adjustment is required on the basis of patient age, body weight, gender, ethnicity, or renal function; or in patients with moderate to severe hepatic impairment due to liver metastases.

CONTRAINDICATIONS

Gefitinib is contraindicated in patients with severe hypersensitivity to gefitinib or to any other component of Gefitinib.

WARNINGS & PRECAUTIONS

Warning

Pulmonary Toxicity: Cases of interstitial lung disease (ILD) have been observed in patients receiving gefitinib at an overall incidence of about 1%. Approximately 1/3 of the cases have been fatal. The reported incidence of ILD was about 2% in the Japanese post-marketing experience, about 0.3% in approximately 23,000 patients treated with gefitinib in a US expanded access program and about 1% in the studies of first-line use in NSCLC (but with similar rates in both treatment and placebo groups). Reports have described the adverse event as interstitial pneumonia, pneumonitis and alveolitis. Patients often present with the acute onset of dyspnea, sometimes associated with cough or low-grade fever, often becoming severe within a short time and requiring hospitalization. ILD has occurred in patients who have received prior radiation therapy (31% of reported cases), prior chemotherapy (57% of reported patients), and no previous therapy (12% of reported cases). Patients with concurrent idiopathic pulmonary fibrosis whose condition worsens while receiving gefitinib have been observed to have an increased mortality compared to those without concurrent idiopathic pulmonary fibrosis.

In the event of acute onset or worsening of pulmonary symptoms (dyspnea, cough, fever), gefitinib therapy should be interrupted and a prompt investigation of these symptoms should occur. If interstitial lung disease is confirmed, gefitinib should be discontinued and the patient treated appropriately.

Precautions

Hepatotoxicity: Asymptomatic increases in liver transaminases have been observed in gefitinib treated patients; therefore, periodic liver function (transaminases, bilirubin, and alkaline phosphatase) testing should be considered. Discontinuation of gefitinib should be considered if changes are severe.

Patients with Hepatic Impairment: In vitro and in vivo evidence suggest that gefitinib is cleared primarily by the liver. Therefore, gefitinib exposure may be increased in patients with hepatic dysfunction. In patients with liver metastases and moderately to severely elevated biochemical liver abnormalities, however, gefitinib pharmacokinetics were similar to the pharmacokinetics of individuals without liver abnormalities. The influence of non-cancer related hepatic impairment on the pharmacokinetics of gefitinib has not been evaluated.

Pediatric Use: Gefitinib is not indicated for use in pediatric patients as safety and effectiveness have not been established. In clinical trials of gefitinib alone or with radiation in pediatric patients with primary Central Nervous System (CNS) tumors, cases of CNS hemorrhage and death have been reported. There are insufficient data in pediatric patients to establish a causal relationship. There is no evidence to suggest increased risk of cerebral hemorrhage in adult patients with NSCLC receiving gefitinib.

Geriatric Use: Of the total number of patients participating in trials of second- and third-line gefitinib treatment of NSCLC, 65% were aged 64 years or less, 30.5 % were aged 65 to 74 years, and 5% of patients were aged 75 years or older. No differences in safety or efficacy were observed between younger and older patients.

Patients with Severe Renal Impairment: The effect of severe renal impairment on the pharmacokinetics of gefitinib is not known. Patients with severe renal impairment should be treated with caution when given gefitinib.

PREGNANCY AND LACTATION

Pregnancy

There are no adequate and well-controlled studies in pregnant women using Gefitinib. If Gefitinib 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 Gefitinib is excreted in human milk.

Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should be advised against breast-feeding while receiving Gefitinib therapy.

ADVERSE EFFECTS

Gastrointestinal disorders: Diarrhoea, · nausea , vomiting ,stomatitis, dehydration, dry mouth

Hepatobiliary disorders: Elevations in alanine aminotransferase, haematuria

Metabolism and nutrition disorders: Anorexia

Skin and subcutaneous tissue disorders: Skin reactions , pustular rash, sometimes itchy with dry skin, including skin fissures on an erythematous base.

General Disorders and administration site conditions: Asthenia

Vascular Disease: Haemorrhage