A patient may have had more than 1 drug-related event.

Table 4: Drug-Related Adverse Events ≥5% at 250 mg does by Worst CTC Grade (n=102)

Adverse Events	(%) of Patients				
	All Grades 1	CTC Grades 2	CTC Grades 3	CTC Grades 4	CTC Grades 5
Diarrhea	48	41	6	1	0
Rash44 (43)	43	39	4	0	0
Acne25 (25)	25	19	6	0	0
Dry skin	13	12	1	0	0
Nausea	13	7	5	1	0
Vomiting	12	9	2	1	0
Pruritus	8	7	1	0	0
Anorexia	7	3	4	0	0
Asthenai	6	2	2	1	1

Other adverse events reported at an incidence of <5% in patients who received either 250 mg or 500 mg as monotherapy for treatment of NSCLC (along with their frequency at the 250 mg recommended dose) include the following: peripheral edema (2%), amblyopia (2%), dyspnea (2%), conjunctivitis (1%), vesiculobullous rash (1%), and mouth ulceration (1%).

Interstitial Lung Disease

Cases of interstitial lung disease (ILD) have been observed in patients receiving GEFITIZ 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 postmarketing experience, about 0.3% in approximately 23,000 patients treated with GEFITIZ 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 GEFITIZ have been observed to have an increased mortality compared to those without concurrent idiopathic pulmonaryfibrosis.

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

In patients receiving GEFITIZ therapy, there were reports of eye pain and corneal erosion/ulcer, sometimes in association with aberrant eyelash growth (see PRECAUTIONS- Information for Patients section). Hemorrhage, such as epistaxis and hematuria have been reported in patients receiving GEFITIZ. There were also rare reports of pancreatitis and very rare reports of corneal membrane sloughing, ocular ischemia/hemorrhage, toxic epidermal necrolysis, erythema multiforme, and allergic reactions, including angioedema and urticaria.

International Normalized Ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin while on GEFITIZ therapy. Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR

Data from non-clinical (in vitro and in vivo) studies indicate that GEFITIZ has the potential to inhibit the cardiac action potential repolarization process (eg, QT interval). The clinical relevance of these findings is unknown.

OVERDOSAGE

The acute toxicity of GEFITIZ up to 500 mg in clinical studies has been low. In nonclinical studies, a single dose of 12,000 mg/m2 (about 80 times the recommended clinical dose on a mg/m2 basis) was lethal to rats. Half this dose caused no mortality in mice.

There is no specific treatment for an GEFITIZ overdose and possible symptoms of overdose are not established. However, in Phase 1 clinical trials, a limited number of patients were treated with daily doses of up to 1000 mg. An increase in frequency and severity of some adverse reactions was observed, mainly diarrhea and skin rash. Adverse reactions associated with overdose should be treated symptomatically; in particular, severe diarrhea should be managed appropriately.

DOSAGE AND ADMINISTRATION

The recommended daily dose of GEFITIZ is one 250 mg tablet with or without food. Higher doses do not give a better response and cause increased toxicity.

For Patients who have Difficulty Swallowing Solids GEFITIZ tablets can also be dispersed in half a glass of drinking water (noncarbonated).

No other liquids should be used. Drop the tablet in the water, without crushing it, stir until the tablet is dispersed (approximately 1O 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-gastrictube.

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), GEFITIZ therapy should be interrupted and a prompt investigation of these symptoms should occur and appropriate treatment initiated. If interstitial lung disease is confirmed, GEFITIZ 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 GEFITIZ 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.

Storage

Store protected from light & moisture, at a temperature not exceeding 30°C.

SHELF LIFE

24 months

HOW SUPPLIED

HDPE Container pack of 30 Tablets

MANUFACTURED & MARKETED BY:

Tizig Pharma Private Limited
Factory: Tukucha, Nala-1, Banepa, Nepal.
Regd. Office: Maligaun-5, Kathmandu, Nepal.

To be sold by retail on prescription of an Oncologist/Cancer hospital/Institution only

GEFITINIB TABLETS IP 250 mg

GEFITIZ 250

Rx only

COMPOSITION

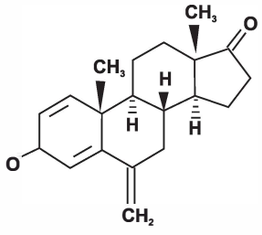
Each film coated tablet contains
Gefitinib IP 250 mg
Excipients q.s.
Colours: Opadry Brown

DESCRIPTION:

GEFITIZ contain 250 mg of Gefitinib and are available as reddish brown color film coated tablets for daily oral administration.

Gefitinib is an anilinoquinazoline with the chemical name 4-Quinazolinamine, N-(3- chloro-4-fluorophenyl)-7-methoxy-6-[3-4-morpholin) propoxy] and the following structural formula:

It has the molecular formula C,,H,.ClFN,O,, a relative molecular mass of 446.9 and is a white-colored powder. GEFITIZ is a free base. The molecule has pKas of 5.4 and 7.2 and therefore ionizes progressively in solution as the pH falls. GEFITIZ can be defined as sparingly soluble at pH 1, but is practically insoluble above pH 7, with the solubility dropping sharply between pH 4 and pH 6. In non-aqueous solvents, GEFITIZ is freely soluble in glacial acetic acid and dimethylsulphoxide, soluble in pyridine, sparingly soluble in tetrahydrofuran, and slightly soluble in methanol, ethanol (99.5%), ethyl acetate, propan-2-ol and acetonitrile.



CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of the clinical antitumor action of GEFITIZ is not fully characterized. GEFITIZ 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. No clinical studies have been performed that demonstrate a correlation between EGFR receptor expression and response to Gefitinib

Pharmacokinetics

Gefitinib is absorbed slowly after oral administration with mean bioavailability of 60%.

Elimination is by metabolism (primarily CYP3A4) and excretion in feces. The elimination half-life is about 48 hours. Daily oral administration of GEFITIZ 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.

GEFITIZ 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. GEFITIZ is extensively distributed throughout the body with a mean steady state volume of distribution of 1400 L following intravenous administration. In vitro binding of GEFITIZ to human plasma proteins (serum albumin and U1-acid glycoprotein) is 90% and is independent of drug concentrations.

Metabolism and Elimination

GEFITIZ 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 GEFITIZ has exposure comparable to GEFITIZ. Although this metabolite has similar EGFR-TK activity to GEFITIZ in the isolated enzyme assay, it had only 1/14 of the potency of GEFITIZ in one of the cell-based assays. GEFITIZ 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.

Special Populations

In population based data analyses, no relationships were identified between predicted steady state trough concentration and patient age, body weight, gender, ethnicity or creatinine clearance.

Pediatric: There are no pharmacokinetic data in pediatric patients.

Hepatic Impairment

The influence of hepatic metastases with elevation of serum aspartate aminotransferase

(AST/SGOT), alkaline phosphatase, and bilirubin has been evaluated in patients with normal (14 patients), moderately elevated (13 patients) and severely elevated (4 patients) levels of one or more of these biochemical parameters. Patients with moderately and severely elevated biochemical liver abnormalities had GEFITIZ pharmacokinetics similar to individuals without liver abnormalities Renal Impairment

No clinical studies were conducted with GEFITIZ in patients with severely compromised renal function .

Drug-Drug Interactions

In human liver microsome studies, GEFITIZ had no inhibitory effect on CYP1A2, CYP2C9, and CYP3A4 activities at concentrations ranging from 2-5000 ng/ml. At the highest concentration studied (5000 ng/mL), GEFITIZ inhibited CYP2C19 by 24% and CYP2D6 by 43%. Exposure to metoprolol, a substrate of CYP2D6, was increased by 30% when it was given in combination with GEFITIZ (500 mg daily for 28 days) in patients with solid tumors. Rifampicin, an inducer of CYP3A4, reduced mean ALIC of GEFITIZ by 85% in healthy male volunteers

Concomitant administration of itraconazole (200 mg QD for 12 days), an inhibitor of CYP3A4, with GEFITIZ (250 mg single dose) to healthy male volunteers, increased mean GEFITIZ ALIC by 88%

Co-administration of high doses of ranitidine with sodium bicarbonate (to maintain the gastric pH above pH 5.0) reduced mean GEFITIZALIC by 44%

International Normalized Ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin while on GEFITIZ therapy. Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR

Clinical Studies

Non-Small Cell Lung Cancer (NSCLC): Refractory Disease Tumor Response Study-A multicenter clinical trial in the United States evaluated the tumor response rate of GEFITIZ in patients with advanced nonsmall cell lung cancer whose disease had progressed after at least two prior chemotherapy regimens including a platinum drug and docetaxel. GEFITIZ was taken once daily at approximately the same time each day.

Two hundred and sixteen patients received GEFITIZ, 102 (47%) and 114 (53%) receiving 250 mg and 500 mg daily doses, respectively. Study patient demographics and disease characteristics are summarized in Table 1. Forty-one percent of the patients had received two prior treatment regimens, 33% three prior treatment regimens, and 25% four or more prior treatment regimens. Effectiveness of GEFITIZ as third line therapy was determined in the 142 evaluable patients with documented disease progression on platinum and docetaxel therapies or who had had unacceptable toxicity on these agents.