WARNINGS

Pulmonary Toxicity

Cases of interstitial lung disease (ILD) have been observed in patients receiving GEFTIWEL® at an overall incidence of about 1 %. Approximately 1/3 of the cases have been fatal. 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 GEFTIWEL® 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) GEFTIWEL ® therapy should be interrupted and a prompt investigation of these symptoms should occur. If interstitial lung disease is confirmed, GEFTIWEL® should be discontinued and the patient treated appropriately.

Pregnancy Category D

GEFTIWEL® may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women using GEFTIWEL® . If GEFTIWEL® 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.

PRECAUTIONS

Hepatotoxicity

Asymptomatic increases in liver transaminases have been observed in GEFTIWEL® treated patients; therefore, periodic liver function (transaminases, bilirubin and alkaline phosphatase) testing should be considered. Discontinuation of GEFTIWEL® 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Gefitinib has been tested for genotoxicity in a series of in vitro (bacterial mutation, mouse lymphoma, and human lymphocyte) assays and an in vivo rat micronucleus test. Under the conditions of these assays, gefitinib did not cause genetic damage.
Carcinogenicity studies have not been conducted with gefitinib.

Pregnancy

Pregnancy Category D.

Nursing Mothers

It is not known whether GEFTIWEL® is excreted in human milk. Following oral administration of carbon-14 labeled gefitinib to rats 14 days postpartum, concentrations of radioactivity in milk were higher than in blood. Levels of gefitinib and its metabolites were 11 to 19 fold higher in milk than in blood, after oral exposure of lactating rats to a dose of 5 mg/kg. 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 GEFTIWEL® therapy.

Pediatric Use

GEFTIWEL® is not indicated for use in pediatric patients as safety and effectiveness have not been established. In clinical trials of GEFTIWEL® 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 GEFTIWEL® .

Geriatric Use

Of the total number of patients participating in trials of second- and third-line GEFTIWEL® 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 GEFTIWEL® .

DRUG INTERACTIONS

Substances that are potent inhibitors of CYP3A4 activity (eg, ketoconazole and itraconazole) decrease gefitinib metabolism and increase gefitinib plasma concentrations. This increase may be clinically relevant as adverse experiences are related to dose and exposure; therefore, caution should be used when administering CYP3A4 inhibitors with GEFTIWEL® . Drugs that cause significant sustained elevation in gastric pH (histamine H2-receptor antagonists such as ranitidine or cimetidine) may reduce plasma concentrations of GEFTIWEL® and therefore potentially may reduce efficacy. Phase II clinical trial data, where GEFTIWEL® and vinorelbine have been used concomitantly, indicate that GEFTIWEL® may exacerbate the neutropenic effect of vinorelbine.

PATIENT INFORMATION

Patients should be advised to seek medical advice promptly if they develop 1) severe or persistent diarrhea, nausea, anorexia, or vomiting, as these have sometimes been associated with dehydration; 2) an onset or worsening of pulmonary symptoms, ie, shortness of breath or cough; 3) an eye irritation; or, 4) any other new symptom.

STORAGE

Store below 30°C. Protect from light and moisture.
Keep out of reach of children.

PRESENTATION

GEFTIWEL® Gefitinib tablets 250 mg available as 3 blisters of 10 tablets each in a box.

Marketed by:
Getwell Oncology Pvt. Ltd.
(A unit of Getwell)
464, Udyog Vihar, Phase-V,
Gurgaon -122 016, Haryana, India.

Manufactured by:
Getwell Pharmaceuticals
Vastrapur, Ahmedabad - 380015,
Gujarat, INDIA.
At: 357, GIDC, Sachin, Surat, Gujarat, INDIA

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For the use only of Registered Medical Practitioner or a Hospital or a Laboratory.

Gefitinib Tablets IP 250 mg

GEFTIWEL®

COMPOSITION

Each film coated tablet contains :

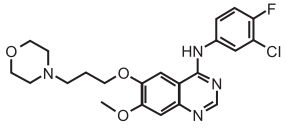
Gefitinib IP	250 mg
Excipients	q.s.

Colours: Yellow Oxide of Iron, Red Oxide of Iron & Titanium Dioxide IP

DESCRIPTION

GEFTIWEL®(gefitinib tablets) contain 250 mg of gefitinib and are available as orange 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 $C_{22}H_{24}ClFN_4O_3$, a relative molecular mass of 446.9 and is a white colored powder. Gefitinib is a free base. The molecule has pKaS of 5.4 and 7.2 and therefore ionizes progressively in solution as the pH falls. Gefitinib 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, gefitinib 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 gefitinib is not fully characterized. 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. 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 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 1 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 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.

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 gefitinib pharmacokinetics similar to individuals without liver abnormalities.

Renal Impairment

No clinical studies were conducted with GEFTIWEL® in patients with severely compromised renal function. Gefitinib and its metabolites are not significantly excreted via the kidney (<4 %).

INDICATIONS

GEFTIWEL® 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 GEFTIWEL®.

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 AND ADMINISTRATION

The recommended daily dose of GEFTIWEL® 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

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

OVERDOSGE

The acute toxicity of gefitinib up to 500 mg in clinical studies has been low. In non-clinical studies, a single dose of 12,000 mg/m^2 (about 80 times the recommended clinical dose on a mg/m^2 basis) was lethal to rats. Half this dose caused no mortality in mice.

There is no specific treatment for an GEFTIWEL® 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.

CONTRAINDICATIONS

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

SIDE EFFECTS

Drug related adverse events with an incidence of ≥5 % for the 216 patients who received either 250 mg or 500 mg of GEFTIWEL® monotherapy for treatment of NSCLC. The most common adverse events reported at the recommended 250 mg daily dose were diarrhea, rash, acne, dry skin, nausea and vomiting. The 500 mg dose showed a higher rate for most of these adverse events.

Drug-related adverse events with an incidence of ≥5 % by CTC grade for the patients who received the 250 mg/day dose of GEFTIWEL® monotherapy for treatment of NSCLC. Only 2 % of patients stopped therapy due to an adverse drug reaction (ADR). The onset of these ADRs occurred within the first month of therapy.

Drug-Related Adverse Events with an Incidence of ≥ 5 % in either 250 mg or 500 mg dose group:

Diarrhea, rash (45 %) were very common, acne (25 %), dry skin, nausea, vomiting was seen in more than 10 % patients, pruritus, anorexia, asthenia, weight loss was observed in few patients (less than 10%).

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 GEFTIWEL® at an overall incidence of about 1 %. Approximately 1/3 of the cases have been fatal. 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 GEFTIWEL® 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) GEFTIWEL® therapy should be interrupted and a prompt investigation of these symptoms should occur. If interstitial lung disease is confirmed, GEFTIWEL® should be discontinued and the patient treated appropriately.

In patients receiving GEFTIWEL® therapy, there were reports of eye pain and corneal erosion/ulcer, sometimes in association with aberrant eyelash growth. Hemorrhage, such as epistaxis and hematuria have been reported in patients receiving GEFTIWEL®. 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 GEFTIWEL® 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 gefitinib has the potential to inhibit the cardiac action potential repolarization process (eg, QT interval). The clinical relevance of these findings is unknown.

Substances that are inducers of CYP3A4 activity increase the metabolism of gefitinib and decrease its plasma concentrations. 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.

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