# Religet™


RELIC
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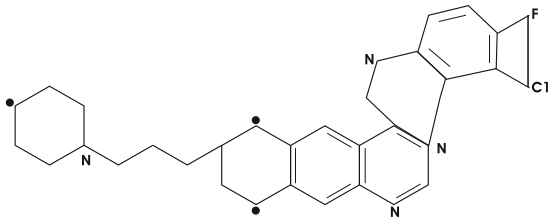
An ISO 9001:2008 Certified Company

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

# RELIGEF (Gefitinib Tablets I.P. 250 mg)

**Composition:**
**Each film coated tablet contains:**
**Gefitinib I.P. 250 mg.**
**Excipients q.s.**

**DESCRIPTION :**
RELIGEF Tablets containing Gefitinib 250 mg are peach colored round shaped film coated tablets. 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 $C_{22}H_{24}$ $ClFN_4$ $O_3$

**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 occuring 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-substitutent on the quinazoline, and oxidative defluorination of the halogenated phenyl group.
Five metabolities 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 bichemical 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 Gefitinib in patients with severely compromised renal function. Gefitinib and its metabolities are not significantly excreted via the kidney(<4%)

**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.

**DOSAGE AND ADMINISTRATION :** The recommended daily dose of RELIGEF is one 250 mg Tablets with or without food. Lesser doses do not give a better response and cause increased toxicity.

**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 (dyspna, cough, fever), Gefitinib therepy 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 Symptomsand 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 carefullymonitored.
No dosage adjustment is required or 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.

**WARNINING :**
Pulmonary Toxicity
please refer adverse event for more details.

**Pregnancy Category D**
Gefitinib may cause fetal harm when administered to a pregnant woman.
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 lose of the pregnancy.

**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 HepaticImpairement**
In vitro and in vivo evidence suggest that Gefitinib is clearly 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 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.

**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 y ears 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.

**DRUG INTERACTIONS**

in human liver microsome is Gefitinib had no inhibitory effect on CYPA2, CYP2C9, and CYP3A4 activities concentrations ranging from 5000 ng/ml. At the highest concentration studied (5000 mg/ml.) Gefitinib inhibite CYP2C 19 by 24% and CYP2D6 by 43%. Exposure to metoprolol, a substrate of CYP2D6, was increased by 30% where it was given in combination with Gefitinib (500 mg daily for 28 days) in patients with solid tumors.

Rifampicin, an inducer of CYP3A4, reduced mean AUC of Gefitinib by 85% in healty male Volunteers. Concomitant administration of itraconazole (200 mg QD for 12 days), an inhibitor of CYP3A4, with Gefitinib (250 mg single dose) to healthy male volunteers, increased mean Gefitinib AUC by 88%

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

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

**ADVERSE REACTIONS**

The safety database includes 941 Patients from clinical trials and approximately 23,000 patients in the Expanded Access program.

Table 1 includes drug-related adverse events with an incidence of 5% for the 216 patients who received either 250 mg or 500 mg of Gefitinib 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.

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

**Table 1:Drug-Related Adverse Events with an incidence of >5% in either 250 mg or 500 mg Dose Group Number (%) of Patients**

| Drug-related adverse event | 250 mg/day (N=102%)% | 500 mg/day (N=114)% |
|---|---|---|
| Diarrhea | 49(48) | 76 (67) |
| Rash | 44(43) | 61 (54) |
| Acne | 25(25) | 37(33) |
| Dry Skin | 13(13) | 30(26) |
| Nausea | 13(13) | 20 (18) |
| Vomiting | 12 (12) | 10 (9) |
| Pruritus | 8(8) | 10 (9) |
| Anorexia | 7(7) | 11 (10) |
| Asthenia | 6 (6) | 5 (4) |
| Weight loss | 3 (3) | 6(5) |

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

Table 2: Drug Related Adverse Events >5% at 250 mg dose by Worst CTC Grade (n=102) % of Patients

| Adverse Event | All Grades | CTC Grade 1 | CTC Grade 2 | CTC Grade 3 | CTC Grade 4 |
|---|---|---|---|---|---|
| Diarrhea | 48 | 41 | 6 | 1 | 0 |
| Rash | 43 | 39 | 4 | 0 | 0 |
| Acne | 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 |
| Asthenia | 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 RELIGEF 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 kpatients 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.

**OTHERS**

In Patients receiving Gefitinib therapy, there were reports of eye pain and corneat erosion/ulcer, sometimes in association with aberrant eyelash growth. Hemorrhage, such as epistaxis and hematuria have been reported in patients receiving Gefitinib. 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 Gefitinib therapy. Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR Data from non-cliinical (invitro and invivo) 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.

**OVERDOSE:**

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 non mortality in mice.

There is no specific treatment for an Gefitinib 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.

**STORAGE:**

Store below 25°C, protect from moisture.

**PRESENTATION**

Blister Pack (1X10's)

RELIGEF