GEFTICIP Tablets (Gefitinib)

**Composition**

GEFTICIP Tablets
Each film coated tablet contains:
Gefitinib............ 250 mg

**Dosage Form**

Oral tablet

**Pharmacology**

**Pharmacodynamics**

The mechanism of the clinical antitumour 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). The epidermal growth factor (EGF) and its receptor (EGFR) have been identified as key drivers in the process of cell growth and proliferation for normal and cancer cells. EGFR activating mutation within a cancer cell is an important factor in promotion of tumour cell growth, blocking of apoptosis, increasing the production of angiogenic factors and facilitating the processes of metastasis.

Gefitinib is a selective small molecule inhibitor of the epidermal growth factor receptor tyrosine kinase and is an effective treatment for patients with tumours with activating mutations of the EGFR tyrosine kinase domain regardless of line of therapy. No clinically relevant activity has been shown in patients with known EGFR mutation-negative tumours.

**Pharmacokinetics**

Gefitinib is absorbed slowly after oral administration, with a mean bioavailability of 60%. Elimination is by metabolism (primarily cytochrome P3A4) and excretion in the faeces. 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 a 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 1,400 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. In a trial in healthy volunteers where gastric pH was maintained above pH 5, gefitinib exposure was reduced by 47 %, likely due to impaired solubility of gefitinib in the stomach.
In vitro data indicate that gefitinib is a substrate for the membrane transport protein Pgp.

**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 one-fourteenth 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 faeces (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.

**Paediatric**

There are no pharmacokinetic data in paediatric 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 gefitinib in patients with severely compromised renal function.

Gefitinib and its metabolites are not significantly excreted via the kidneys (<4%)

**Drug-Drug Interactions**

In human liver microsome studies, gefitinib had no inhibitory effect on CYP1A2, CYP2C9 and CYP3A4 activities at concentrations ranging from 2 to 5,000 ng/mL. At the highest concentration studied (5,000 ng/mL), gefitinib 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 gefitinib (500 mg daily for 28 days) in patients with solid tumours.

Rifampicin, an inducer of CYP3A4, reduced the mean AUC of gefitinib by 85% in healthy 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 the 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 the 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.

## Indications

GEFTICIP Tablets are indicated as monotherapy for the continued treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of both platinum-based and
docetaxel chemotherapies who are benefiting or have benefited from GEFTICIP Tablets. 
GEFTICIP Tablets are indicated for the treatment of adult patients with locally advanced or metastatic NSCLC with activating mutations of EGFR-TK.

In light of the positive survival data with other agents, including another oral EGFR inhibitor, physicians should use other treatment options in advanced NSCLC patient populations who have received one or two prior chemotherapy regimens and are refractory or intolerant to their most recent regimen. 
The effectiveness of GEFTICIP Tablets was initially based on objective response rates. Subsequent studies intended to demonstrate an increase in survival have been unsuccessful. Specifically, results from a large placebo-controlled randomized trial in patients with advanced NSCLC who progressed while receiving chemotherapy or within 90 days of the last dose of chemotherapy or were intolerant to the most recent prior chemotherapy regimen, did not show an improvement in survival.

Results from two large, controlled, randomized trials in the first-line treatment of NSCLC showed no benefit from adding GEFTICIP Tablets to doublet, platinum-based chemotherapy.

**Dosage And Administration**

The recommended daily dose of GEFTICIP Tablets is one 250 mg tablet with or without food. Higher doses do not give a better response and cause increased toxicity. If a dose of GEFTICIP Tablets is missed, it should be taken as soon as the patient remembers. If it is less than 12 hours to the next dose, the patient should not take the missed dose. Patients should not take a double dose (two doses at the same time) to make up for a forgotten dose.

**Dosage Adjustment**

Patients with poorly tolerated diarrhoea (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 (dyspnoea, cough, fever), GEFTICIP Tablets therapy should be interrupted and a prompt investigation of these symptoms should occur and appropriate treatment initiated. If interstitial lung disease (ILD) is confirmed, GEFTICIP Tablets should be discontinued and the patient treated appropriately.

Patients who develop an onset of eye symptoms such as pain should be medically evaluated and managed appropriately, including interruption of GEFTICIP Tablets therapy and removal of an aberrant eyelash, if present. After the 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 reactions, 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.

**Paediatric Population**

The safety and efficacy of GEFTICIP Tablets in children and adolescents aged less than 18 years has not been established. There is no relevant use of GEFTICIP Tablets in the paediatric population in the indication of NSCLC.

**Hepatic Impairment**

Patients with moderate-to-severe hepatic impairment (Child-Pugh B or C) due to cirrhosis have increased plasma concentrations of gefitinib. These patients should be closely monitored for adverse events. Plasma
concentrations were not increased in patients with elevated aspartate transaminase (AST), alkaline phosphatase or bilirubin due to liver metastases.

Renal Impairment
No dose adjustment is required in patients with impaired renal function at creatinine clearance >20 ml/min. Only limited data are available in patients with creatinine clearance ≤20 ml/min and caution is advised in these.

Elderly
No dose adjustment is required on the basis of the patient's age.

CYP2D6 Poor Metabolizers
No specific dose adjustment is recommended in patients with known CYP2D6 poor metabolizer genotype, but these patients should be closely monitored for adverse events.

Dose Adjustment Due to Toxicity
Patients with poorly tolerated diarrhoea or skin adverse reactions may be successfully managed by providing a brief (up to 14 days) therapy interruption followed by reinstatement of the 250 mg dose. For patients unable to tolerate treatment after a therapy interruption, GEFTICIP Tablets should be discontinued and an alternative treatment should be considered.

**Contraindications**

GEFTICIP Tablets are contraindicated in patients with a severe hypersensitivity to gefitinib or to any other component of GEFTICIP Tablets.
GEFTICIP Tablets are contraindicated in lactating women.

**Warnings And Precautions**

**Assessment of EGFR Mutation Status**

When assessing the EGFR mutation status of a patient, it is important that a well-validated and robust methodology is chosen to avoid false-negative or false-positive determinations.

**Drug Interactions**

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 phenytoin, carbamazepine, rifampicin, barbiturates or herbal preparations containing St John's wort (*Hypericum perforatum*), a dose increase to 500 mg daily should be considered in the absence of severe adverse drug reactions, and clinical response and adverse events should be carefully monitored. Pre-treatment with rifampicin (a potent CYP3A4 inducer) in healthy volunteers reduced the mean gefitinib AUC by 83%.

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. Substances that are potent inhibitors of CYP3A4 activity (e.g. ketoconazole, itraconazole, posaconazole, voriconazole, protease inhibitors, clarithromycin, telithromycin etc.) 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 gefitinib. The increase might be higher in individual patients with CYP2D6 poor metabolizer genotype. Pre-treatment with itraconazole (a potent CYP3A4 inhibitor) resulted in an 80% increase in the mean AUC of gefitinib in healthy volunteers. In situations of concomitant treatment with potent inhibitors of CYP3A4, the patient should be closely monitored for gefitinib adverse reactions.
There are no data on concomitant treatment with an inhibitor of CYP2D6, but potent inhibitors of this enzyme might cause increased plasma concentrations of gefitinib in CYP2D6 extensive metabolizers by about 2-fold. If concomitant treatment with a potent CYP2D6 inhibitor is initiated, the patient should be closely monitored for adverse reactions.

Drugs that cause significant sustained elevation in gastric pH, such as proton-pump inhibitors and histamine H₂-receptor antagonists such as ranitidine or cimetidine may reduce plasma concentrations of gefitinib and, therefore, may potentially reduce efficacy. High doses of short-acting antacids may have a similar effect if taken regularly close in time to the administration of gefitinib. Concomitant administration of gefitinib with ranitidine at a dose that caused sustained elevations in gastric pH ≥5 resulted in a reduced mean gefitinib AUC by 47% in healthy volunteers.

Phase II clinical trial data, where gefitinib and vinorelbine have been used concomitantly, indicate that gefitinib may exacerbate the neutropenic effect of vinorelbine.

**Active Substances That May Have Their Plasma Concentrations Altered by Gefitinib**

*In vitro* studies have shown that gefitinib has limited potential to inhibit CYP2D6. In a clinical trial in patients, gefitinib was co-administered with metoprolol (a CYP2D6 substrate). This resulted in a 35% increase in exposure to metoprolol. Such an increase might potentially be relevant for CYP2D6 substrates with a narrow therapeutic index. When the use of CYP2D6 substrates are considered in combination with gefitinib, a dose modification of the CYP2D6 substrate should be considered, especially for products with a narrow therapeutic window.

Gefitinib inhibits the transporter protein, BCRP, *in vitro*, but the clinical relevance of this finding is unknown.

**Pulmonary Toxicity**

Cases of ILD have been observed in patients receiving gefitinib at an overall incidence of about 1%. Approximately one-third 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 gefitinib in a US expanded access programme 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 dyspnoea, 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 (dyspnoea, cough, fever), gefitinib therapy should be interrupted and a prompt investigation of these symptoms should occur. If ILD is confirmed, gefitinib should be discontinued and the patient treated appropriately.

In a Japanese pharmaco-epidemiological case control study in 3,159 patients with NSCLC receiving gefitinib or chemotherapy who were followed up for 12 weeks, the following risk factors for developing ILD (irrespective of whether the patient received gefitinib or chemotherapy) were identified: smoking, poor performance status (PS ≥2), CT scan evidence of reduced normal lung (≤50%), recent diagnosis of NSCLC (<6 months), pre-existing ILD, older age (≥55 years old) and concurrent cardiac disease. An increased risk of ILD on gefitinib relative to chemotherapy was seen predominantly during the first 4 weeks of treatment (adjusted odds ratio, 3.8; 95% confidence interval, 1.9–7.7); thereafter the relative risk was lower (adjusted OR, 2.5; 95% CI, 1.1–5.8). Risk of mortality among patients who developed ILD on gefitinib or
Chemotherapy was higher in patients with the following risk factors: smoking, CT scan evidence of reduced normal lung (≤50%), pre-existing ILD, older age (≥65 years old), and extensive areas adherent to pleura (≥50%).

**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.

Women of childbearing potential must be advised not to get pregnant during therapy.

**Lactose**

Gefitinib contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp-lactose deficiency or glucose-galactose malabsorption should not take this medicinal product.

**Hepatotoxicity**

Liver function test abnormalities (including increases in alanine aminotransferase (ALT), AST, bilirubin) have been observed, uncommonly presenting as hepatitis. There have been isolated reports of hepatic failure, which, in some cases, led to fatal outcomes. Therefore, periodic liver function (transaminases, bilirubin and alkaline phosphatase) testing is recommended. Gefitinib should be used cautiously in the presence of mild-to-moderate changes in liver function. Discontinuation should be considered if the changes are severe. Impaired liver function due to cirrhosis has been shown to lead to increased plasma concentrations of gefitinib.

**Information for Patients**

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

**Further Precautions for Use**

Patients should be advised to seek medical advice immediately if they experience:

- Severe or persistent diarrhoea, nausea, vomiting or anorexia as these may indirectly lead to dehydration. These symptoms should be managed as clinically indicated.
- Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.
- If a diagnosis of ulcerative keratitis is confirmed, treatment with gefitinib should be interrupted, and if symptoms do not resolve, or if symptoms recur on reintroduction of gefitinib, permanent discontinuation should be considered.
- In a phase I/II trial studying the use of gefitinib and radiation in paediatric patients, with newly diagnosed brain stem glioma or incompletely resected supratentorial malignant glioma, 4 cases (1 fatal) of Central Nervous System (CNS) haemorrhages were reported from 45 patients enrolled. A further case of CNS haemorrhage has been reported in a child with an ependymoma from a trial with gefitinib alone. An increased risk of cerebral haemorrhage in adult patients with NSCLC receiving gefitinib has not been established.
- Gastrointestinal perforation has been reported in patients taking gefitinib. In most cases this is associated with other known risk factors, including concomitant medications such as steroids or NSAIDs, underlying history of GI...
ulceration, age, smoking or bowel metastases at sites of perforation.

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.

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 was 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.

Pregnancy

Pregnancy Category D

There are no data from the use of gefitinib in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Gefitinib should not be used during pregnancy unless clearly necessary. 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 foetus or potential risk for loss of the pregnancy.

Lactation

It is not known whether gefitinib is excreted in human milk. Following oral administration of carbon-14 labelled 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 the 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 breastfeeding while receiving gefitinib therapy. Gefitinib is contraindicated during breast-feeding.

Paediatric Use

Gefitinib is not indicated for use in paediatric patients as safety and effectiveness have not been established. In clinical trials of gefitinib alone or with radiation in paediatric patients with primary central nervous system (CNS) tumours, cases of CNS haemorrhage and death have been reported. There are insufficient data in paediatric patients to establish a causal relationship. There is no evidence to suggest increased risk of cerebral haemorrhage 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.

Effects on the Ability to Drive and Use Machines

Gefitinib has no or negligible influence on the ability to drive and use machines. However, during treatment with gefitinib, asthenia has been reported. Therefore, patients who experience this symptom should be cautious when driving or using machines.

Undesirable Effects
In the pooled dataset from the ISEL, INTEREST and IPASS Phase III clinical trials (2,462 gefitinib-treated patients), the most frequently reported adverse drug reactions, occurring in more than 20% of the patients, are diarrhoea and skin reactions (including rash, acne, dry skin and pruritus). Adverse drug reactions usually occur within the first month of therapy and are generally reversible. Approximately 8% of patients had a severe adverse drug reaction (common toxicity criteria, grade 3 or 4). Approximately 3% of patients stopped therapy due to an adverse drug reaction.

ILD, often severe (CTC grade 3-4), has occurred in 1.3% of patients. Cases with fatal outcomes have been reported.

The safety profile presented in Table 1 is based on the gefitinib clinical development programme and postmarketing experience. Adverse reactions have been assigned to the frequency categories in Table 1 where possible, based on the incidence of comparable adverse event reports in a pooled dataset from the ISEL, INTEREST and IPASS Phase III clinical trials (2,462 gefitinib-treated patients). Frequencies of occurrence of undesirable effects are defined as: very common (1/10); common (>1/100 to <1/10); uncommon (1/1,000 to <1/100); rare (1/10,000 to <1/1,000); very rare (<1/10,000), and not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The 500 mg dose showed a higher rate for most of these adverse events.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Very common</td>
<td>Anorexia, mild or moderate (CTC grade 1 or 2)</td>
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<tr>
<td></td>
<td>Common</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Common</td>
<td>Conjunctivitis, blepharitis, and dry eye*, mainly mild (CTC grade 1)</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Corneal erosion, reversible and sometimes in association with aberrant eyelash growth</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Corneal membrane sloughing, ocular ischaemia/haemorrhage</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Common</td>
<td>Haemorrhage, such as epistaxis and haematuria</td>
</tr>
</tbody>
</table>
Respiratory, thoracic and mediastinal disorders

Common
ILD (1.3%), often severe (CTC grade 3-4). Cases with fatal outcomes have been reported.

Gastrointestinal disorders

Very common
Diarrhoea, mainly mild or moderate (CTC grade 1 or 2)

Vomiting, mainly mild or moderate (CTC grade 1 or 2)

Nausea, mainly mild (CTC grade 1)

Stomatitis, predominantly mild in nature (CTC grade 1)

Common
Dehydration, secondary to diarrhoea, nausea, vomiting or anorexia

Dry mouth*, predominantly mild (CTC grade 1)

Uncommon
Pancreatitis, gastrointestinal perforation

Hepatobiliary disorders

Very common
Elevations in ALT, mainly mild to moderate

Common
Elevations in AST, mainly mild to moderate

Elevations in total bilirubin, mainly mild to moderate

Uncommon
Hepatitis***
| Skin and subcutaneous tissue disorders | Very common | Skin reactions, mainly a mild or moderate (CTC grade 1 or 2) pustular rash, sometimes itchy with dry skin, including skin fissures, on an erythematous base |
| Common | Nail disorder |
| Alopecia |
| Uncommon | Allergic reactions**, including angio-oedema and urticaria |
| Rare | Bullous conditions, including toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme |
| Cutaneous vasculitis |
| Renal and urinary disorders | Common | Asymptomatic laboratory elevations in blood creatinine |
| Proteinuria |
| Cystitis |
| Rare | Haemorrhagic cystitis |
| General disorders | Very common | Asthenia, predominantly mild (CTC grade 1) |
| Common | Pyrexia |

Frequency of adverse drug reactions relating to abnormal laboratory values is based on patients with a change in baseline of 2 or more CTC grades in the relevant laboratory parameters.

*This event can occur in association with other dry conditions (mainly skin reactions) seen with gefitinib.

**The overall incidence of adverse events of allergic reaction reported in the pooled analysis of the ISEL, INTEREST and IPASS trials was 1.5% (36 patients). Of the 36 patients, 14 were excluded from the reported frequency as their reports contained evidence of either a non-allergic aetiology or that the allergic reaction was the result of treatment with another medicinal product.

***This includes isolated reports of hepatic failure, which, in some cases, led to fatal outcomes. 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 oedema (2%), amblyopia (2%), dyspnoea (2%), conjunctivitis (1%), vesiculobullous rash (1%), and mouth ulceration (1%).
ILD
In the INTEREST trial, the incidence of ILD-type events was 1.4% (10) patients in the gefitinib group versus 1.1% (8) patients in the docetaxel group. One ILD-type event was fatal, and this occurred in a patient receiving gefitinib.

In the ISEL trial, the incidence of ILD-type events in the overall population was approximately 1% in both treatment arms. The majority of ILD-type events reported were from patients of Asian ethnicity and the ILD incidence among patients of Asian ethnicity receiving gefitinib therapy and placebo was approximately 3% and 4%, respectively. One ILD-type event was fatal, and this occurred in a patient receiving placebo.

In a postmarketing surveillance study in Japan (3,350 patients), the reported rate of ILD-type events in patients receiving gefitinib was 5.8%. The proportion of ILD-type events with a fatal outcome was 38.6%.

In a Phase III open-label clinical trial (IPASS) in 1,217 patients comparing gefitinib to carboplatin/paclitaxel doublet chemotherapy as first-line treatment in selected patients with advanced NSCLC in Asia, the incidence of ILD-type events was 2.6% on the gefitinib treatment arm versus 1.4% on the carboplatin/paclitaxel treatment arm.

Preclinical Safety Data
Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to the clinical exposure levels and with possible relevance to clinical use were as follows:

- Corneal epithelia atrophy and corneal translucencies
- Renal papillary necrosis
- Hepatocellular necrosis and eosinophilic sinusoidal macrophage infiltration

Data from in vitro studies indicate that gefitinib has the potential to inhibit cardiac repolarization (e.g. QT interval). The clinical significance of these findings is unknown.

A reduction in female fertility was observed in the rat at a dose of 20 mg/kg/day.

Published studies have shown that genetically modified mice, lacking expression of EGFR, exhibit developmental defects related to epithelial immaturity in a variety of organs, including the skin, gastrointestinal tract and lungs. When gefitinib was administered to rats during organogenesis, there were no effects on the embryo-foetal development at the highest dose (30 mg/kg/day). However, in the rabbit, there were reduced foetal weights at 20 mg/kg/day and above. There were no compound-induced malformations in either species. When administered to the rat throughout gestation and parturition, there was a reduction in pup survival at a dose of 20 mg/kg/day.

Following oral administration of C-14 labelled gefitinib to lactating rats 14 days.

Postpartum, concentrations of radioactivity in milk were 11- to 19-fold higher than in blood.

Gefitinib showed no genotoxic potential.

A 2-year carcinogenicity study in rats resulted in a small but statistically significant increased incidence of hepatocellular adenomas in both male and female rats and mesenteric lymph node haemangiosarcomas in female rats at the highest dose (10 mg/kg/day) only. The hepatocellular adenomas were also seen in a 2-year carcinogenicity study in mice, which demonstrated a small increased incidence of this finding in male mice at the mid dose, and in both male and female mice at the highest dose. The effects reached statistical significance for the female mice, but not for the males. At no-effect levels in both mice and rats, there was no margin in clinical exposure. The clinical relevance of these findings is unknown.

The results of an in vitro phototoxicity study demonstrated that gefitinib may have phototoxicity potential.

Overdosage
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/m² (about 80 times the recommended clinical dose on an mg/m² basis) was lethal to rats. Half this dose caused no mortality in mice. There is no specific treatment for a 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 1,000 mg. An increase in the frequency and severity of some adverse reactions was observed, mainly diarrhoea and skin rash. Adverse reactions associated with overdose should be treated symptomatically; in particular, severe diarrhoea should be managed appropriately. In one study a limited number of patients were treated weekly with doses from 1500 mg to 3500 mg. In this study gefitinib exposure did not increase with increasing dose, adverse events were mostly mild to moderate in severity, and were consistent with the known safety profile of gefitinib.

**Shelf-Life**

2 years

**Storage And Handling Instructions**

Store in a cool dry place. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**Packaging Information**

GEFTICIP-250 Tablets: Container pack of 10 Capsules
GEFTICIP-250 Tablets: Container pack of 30 Capsules

*Last updated: January 2013*

*Last reviewed: November 2013*

GEFTICIP Tablets

Source URL: https://ciplamed.com/content/gefticip-tablets