For the use of oncologist or a hospital or a laboratory only 8029839-9093

GEFTIFOS 250

(Gefitinib Tablets I.P.)

COMPOSITION

GEFTIFOS 250

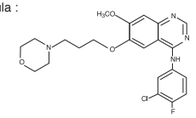
Each film coated tablet contains :

Gefitinib I.P. 250 mg

Colours : Aluminium Lake of Sunset Yellow and Titanium Dioxide I.P.

DESCRIPTION

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



It has the molecular formula $C_{22}H_{24}O_3N_4FCl$, 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. Gefitinib is freely soluble in glacial acetic acid and dimethylsulphoxide.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

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 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 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, moderately elevated and severely elevated 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 kidney (< 4%).

INDICATIONS

Gefitinib is Indicated for the treatment of non small cell lung cancer (NSLC) in adult patients.

DOSE AND METHOD OF ADMINISTRATION

Treatment with gefitinib should be initiated and supervised by a physician experienced in the use of anticancer therapies.

Dosage

The recommended dosage of gefitinib is one 250 mg tablet once a day. If a dose of gefitinib 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.

Paediatric population

The safety and efficacy of gefitinib in children and adolescents aged less than 18 years have not been established. There is no relevant use of gefitinib 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 patients.

Elderly

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

CYP2D6 poor metabolisers

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

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.

Method of administration

The tablet may be taken with or without food, at about the same time each day. The tablet can be swallowed whole with water.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

Breast-feeding

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.

Interstitial lung disease (ILD)

ILD, which may be acute in onset, has been observed in 1.3 % of patients receiving gefitinib, and some cases have been fatal. If patients experience worsening of respiratory symptoms such as dyspnoea, cough and fever, gefitinib should be interrupted and the patient should be promptly investigated. If ILD is confirmed, gefitinib should be discontinued and the patient treated appropriately.

Hepatotoxicity and liver impairment

Liver function test abnormalities (including increases in alanine aminotransferase, aspartate aminotransferase, and 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 testing is recommended. Gefitinib should be used cautiously in the presence of mild to moderate changes in liver function. Discontinuation should be considered if changes are severe. Impaired liver function due to cirrhosis has been shown to lead to increased plasma concentrations of gefitinib.

Interactions with other medicinal products

CYP3A4 inducers may increase metabolism of gefitinib and decrease gefitinib plasma concentrations. Therefore, concomitant administration of CYP3A4 inducers (e.g. phenytoin, carbamazepine, rifampicin, barbiturates or herbal preparations containing St John's wort/Hypericum perforatum) may reduce efficacy of the treatment and should be avoided. In individual patients with CYP2D6 poor metaboliser genotype, treatment with a potent CYP3A4 inhibitor might lead to increased plasma levels of gefitinib. At initiation of treatment with a CYP3A4 inhibitor, patients should be closely monitored for gefitinib adverse reactions.

International normalised ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin together with gefitinib. Patients taking warfarin and gefitinib concomitantly should be monitored regularly for changes in prothrombin time (PT) or INR.

Medicinal products that cause significant sustained elevation in gastric pH, such as proton-pump inhibitors and H_2-antagonists may reduce bioavailability and plasma concentrations of gefitinib and, therefore, may reduce efficacy. Antacids if taken regularly close in time to administration of gefitinib may have a similar effect.

Lactose

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

Further precautions for use

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

- Any eye symptoms.
- Severe or persistent diarrhoea, nausea, vomiting or anorexia as these may indirectly lead to dehydration.

These symptoms should be managed as clinically indicated.

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.

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 lung. When gefitinib was administered to rats during organogenesis, there were no effects on embryofoetal 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 post partum, concentrations of radioactivity in milk were 11-19 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 might have phototoxicity potential.

DRUG INTERACTIONS

The metabolism of gefitinib is via the cytochrome P450 isoenzyme CYP3A4 (predominantly) and via CYP2D6.

Active substances that may increase gefitinib plasma concentrations

In vitro studies have shown that gefitinib is a substrate of p-glycoprotein (Pgp). Available data do not suggest any clinical consequences to this in vitro finding. Substances that inhibit CYP3A4 may decrease the clearance of gefitinib. Concomitant administration with potent inhibitors of CYP3A4 activity (e.g. ketoconazole, posaconazole, voriconazole, protease inhibitors, clarithromycin, and telithromycin) may increase gefitinib plasma concentrations. The increase may be clinically relevant since adverse reactions are related to dose and exposure. The increase might be higher in individual patients with CYP2D6 poor metaboliser 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 metabolisers by about 2-fold. If concomitant treatment with a potent CYP2D6 inhibitor is initiated, the patient should be closely monitored for adverse reactions.

Active substances that may reduce gefitinib plasma concentrations

Substances that are inducers of CYP3A4 activity may increase metabolism and decrease gefitinib plasma concentrations and thereby reduce the efficacy of gefitinib. Concomitant medicinal products that induce CYP3A4 (e.g. phenytoin, carbamazepine, rifampicin, barbiturates or St John's wort (Hypericum perforatum)), should be avoided. Pre-treatment with rifampicin (a potent CYP3A4 inducer) in healthy volunteers reduced mean gefitinib AUC by 83 %. Substances that cause significant sustained elevation in gastric pH may reduce gefitinib plasma concentrations and thereby reduce the efficacy of gefitinib. High doses of short-acting antacids may have a similar effect if taken regularly close in time to 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. 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 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.

Other potential interactions

INR elevations and/or bleeding events have been reported in some patients concomitantly taking warfarin.

ADVERSE EFFECTS

In the pooled dataset from the ISEL, INTEREST and IPASS phase III clinical trials, the most frequently reported adverse drug reactions (ADRs), occurring in more than 20 % of the patients, are diarrhoea and skin reactions (including rash, acne, dry skin and pruritus). ADRs usually occur within the first month of therapy and are generally reversible. Approximately 8 % of patients had a severe ADR (common toxicity criteria, (CTC) grade 3 or 4). Approximately 3 % of patients stopped therapy due to an ADR. Interstitial lung disease (ILD) has occurred in 1.3 % of patients, often severe (CTC grade 3-4). Cases with fatal outcomes have been reported. The safety profile presented in Table 1 is based on the gefitinib clinical development programme and postmarketed 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.

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), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table1 : Adverse reactions

Adverse reactions by system organ class and frequency		
Metabolism and Nutrition disorders	Very Common	Anorexia mild or moderate (CTC grade 1 or 2).
Eye disorders	Common	Conjunctivitis, blepharitis, and dry eye*, mainly mild (CTC grade 1).
	Uncommon	Corneal erosion, reversible and sometimes in association with aberrant eyelash growth.
Vascular disorders	Common	Haemorrhage, such as epistaxis and haematuria.
Respiratory, thoracic and mediastinal disorders	Common	Interstitial lung disease (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 alanine aminotransferase, mainly mild to moderate.
	Common	Elevations in aspartate aminotransferase, 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 angioedema 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 ADRs 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 %.

***This includes isolated reports of hepatic failure which in some cases led to fatal outcomes.

Interstitial lung disease (ILD)

In the INTEREST trial, the incidence of ILD type events was 1.4 % patients in the gefitinib group vs. 1.1 % 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 post-marketing surveillance study in Japan 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) 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.

PREGNANCY AND LACTATION

Women of childbearing potential

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

Pregnancy

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.

Breastfeeding

It is not known whether gefitinib is secreted in human milk. Gefitinib and metabolites of gefitinib accumulated in milk of lactating rats. Gefitinib is contraindicated during breast-feeding and therefore breast-feeding must be discontinued while receiving Gefitinib therapy.

OVERDOSAGE

There is no specific treatment in the event of overdose of gefitinib. However, in phase I clinical trials, a limited number of patients were treated with daily doses of up to 1000 mg. An increase of 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 as clinically indicated. 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.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE :

Store below 25°C, protected from light and moisture.

Keep out of reach of children.

PRESENTATION:

GEFTIFOS 250 is available as blister strip of 10 tablets.

torrent

Marketed by :

TORRENT PHARMACEUTICALS LTD.

Indrad-382 721, Dist. Mehsana, INDIA.

Manufactured by :

Naprod Life Sciences Pvt. Ltd.

G-17/1, M.I.D.C., Tarapur Industrial Area Boisar,

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