Gefinix
Gefitinib

COMPOSITION
Gefinix Tablet: Each tablet contains Gefitinib INN 250 mg.

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.

PHARMACOKINETICS
Absorption
Following oral administration of Gefitinib, absorption is moderately slow and peak plasma concentrations of Gefitinib typically occur at 3 to 7 hours after administration. Mean absolute bioavailability is 59% in cancer patients. Exposure to Gefitinib is not significantly altered by food. 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

Distribution
Gefitinib has a mean steady state volume of distribution of 1400L indicating extensive distribution into tissue. Plasma protein binding is approximately 90%. Gefitinib binds to serum albumin and alpha 1-acid glycoprotein. In vitro data indicates that Gefitinib is a substrate for the membrane transport protein Pgp.

Metabolism
In vitro data indicates that CYP3A4 and CYP2D6 are the major P450 isozyme involved in the oxidative metabolism of Gefitinib. It is therefore considered unlikely that it contributes to the clinical activity of Gefitinib. The formation of O-desmethyl Gefitinib has been shown, in vitro to be via CYP2D6.

Elimination
Gefitinib is excreted mainly as metabolites via the faeces, with renal elimination of Gefitinib and metabolites accounting for less than 4% of the administered dose. Gefitinib total plasma clearance is approximately 500 ml/min and the mean terminal half-life is 41 hours in cancer patients. Administration of Gefitinib once daily results in 2 to 8-fold accumulation.

INDICATIONS AND USAGE
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.
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 Gefinix is one tablet with or without food. Higher doses do not give a better response and cause increased toxicity.

METHOD OF ADMINISTRATION
The tablet may be taken with or without food, at about the same time each day

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

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

SIDE EFFECTS
Respiratory
Patients with ILD usually present with the acute onset of dyspnea which is sometimes associated with cough or low grade fever. The condition often becomes severe within a short time and requires hospitalization. ILD has been reported in patients who have received prior radiation (31% of reported cases), prior chemotherapy (57% of reported cases) and no previous therapy (12% of reported cases).

Gastrointestinal
Gastrointestinal side effects including diarrhea (up to 67%), nausea (up to 18%), vomiting (up to 12 %) and mouth ulceration (1%) have been reported. Pancreatitis (0.1%) has been reported rarely.

Dermatologic
Dermatologic side effects including rash (up to 54%), acne (up to 33%), dry skin (up to 26%), pruritus (up to 9%) and vesiculobullous rash (1%) have been reported. Toxic epidermal necrolysis and erythema multiforme have been reported very rarely. Three cases of hand-foot syndrome recall have been reported. Two cases of acute generalized exanthematous pustulosis have been reported. A case of terminal hair growth on the nose tip, a case of nonscarring inflammatory alopecia, a case of scarring alopecia, a case of sycosis with pyoderma gangrenosum-like lesions and a case of pyogenic granuloma-like lesions of the nail have also been reported. Hand-foot syndrome can occur in patients who have been previously exposed to agents known to cause hand-foot syndrome.

General
General side effects including anorexia (up to 10%), asthenia (up to 6%) and weight loss (up to 5%) have been reported.

Cardiovascular
Cardiovascular side effects including peripheral edema (2%) have been reported.

Ocular
Ocular side effects including amblyopia (2%) and conjunctivitis (1%) have been reported. Eye pain and corneal erosion/ulcer (sometimes associated with aberrant eyelash growth) have also been reported. Corneal membrane sloughing and ocular ischemia/hemorrhage have been reported very rarely.

Hypersensitivity
Hypersensitivity side effects including angioedema and urticaria have been reported very rarely.

Nervous system
There is insufficient data in pediatric patients to establish a causal relationship. Furthermore, there is no evidence to suggest an increased risk of cerebral hemorrhage in adult patients with NSCLC receiving Gefitinib (Nervous system side effects have included cases of CNS hemorrhage and death in pediatric patients with primary central nervous system tumors).

Renal
Renal side effects including hematuria have been reported. A case of nephrotic syndrome has also been reported.

DRUG INTERACTION
In human liver microsome studies, Gefitinib had no inhibitory effect on CYP1A2, CYP2C9 and CYP3A4 activities at concentrations ranging from 2-5000 ng/mL. At the highest concentration studied (5000 ng/mL), 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 tumors.
Rifampicin, an inducer of CYP3A4, reduced 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 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% (see International Normalized Ratio (INR) elevations and/or bleeding events have been reported in some patients taking Warferin while on Gefitinib therapy. Patients taking Warferin should be monitored regularly for changes in prothrombin time or INR.

USE IN SPECIFIC POPULATION

Pregnancy Category D
Gefitinib may cause fetal harm when administered to a pregnant woman. A single dose study in rats showed that Gefitinib crosses the placenta after an oral dose of 5 mg/kg (30 mg/m^2, about 1/5 the recommended human dose on a mg/m^2 basis). There are no adequate and well-controlled studies in pregnant women using Gefinix. If Gefinix 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.

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.

Nursing Mothers
It is not known whether Gefitinib 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.

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 no 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.

PHARMACEUTICAL INFORMATION
Storage Condition
Store in a cool and dry place, away from light. Keep out of the reach of children.

Presentation & Packaging
Gefinix Tablet: Each commercial box contains 30 tablets in Alu-Alu blister pack.

Manufactured By
BEACON
Pharmaceuticals Limited
Mymensingh, Bangladesh

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