Erlonix

Erlotinib 100 mg & 150 mg

COMPOSITION
Erlonix 100 Tablet : Each film coated tablet contains Erlotinib Hydrochloride INN equivalent to Erlotinib 100 mg.

Erlonix 150 Tablet : Each film coated tablet contains Erlotinib Hydrochloride INN equivalent to Erlotinib 150 mg.

CLINICAL PHARMACOLOGY
Erlotinib potently inhibits the intracellular phosphorylation of HER1/EGFR receptor. HER1/EGFR receptor is expressed on the cell surface of normal cells and cancer cells. In non-clinical models, inhibition of EGFR phosphotyrosine results in cell stasis and/or death.

Pharmacodynamics/Kinetics

Absorption
Oral erlotinib is well absorbed and has an extended absorption phase, with mean peak plasma levels occurring at 4 hours after oral dosing. A study in normal healthy volunteers provided an estimate of bioavailability of 59%. The exposure after an oral dose may be increased by food.

Following absorption, erlotinib is highly bound in blood, with approximately 95% bound to blood components, primarily to plasma proteins (i.e. albumin and alpha-1 acid glycoprotein [AAG]), with a free fraction of approximately 5%.

Distribution
Erlotinib has a mean apparent volume of distribution of 232 L and distributes into tumour tissue of humans. In a study of 4 patients (3 with NSCLC and 1 with laryngeal cancer) receiving 150 mg daily oral doses of Erlotinib, tumour samples from surgical excisions on Day 9 of treatment revealed tumour concentrations of erlotinib that averaged 1,185 ng/g of tissue. This corresponded to an overall average of 63% of the steady state observed peak plasma concentrations. The primary active metabolites were present in tumours at concentrations averaging 160 ng/g tissue, which corresponded to an overall average of 113% of the observed steady state peak plasma concentrations. Tissue distribution studies using whole body autoradiography following oral administration with [14C] labelled erlotinib in athymic nude mice with HN5 tumour xenografts have shown rapid and extensive tissue distribution with maximum concentrations of radiolabelled erlotinib (approximately 73% of that in plasma) observed at 1 hour.

Metabolism
Erlotinib is metabolised in humans by hepatic cytochrome P450 enzymes, primarily by CYP3A4 and to a lesser extent by CYP1A2. Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung and CYP1B1 in tumour tissue potentially contribute to the metabolic clearance of erlotinib. In vitro studies indicate approximately 80 - 95% of erlotinib metabolism is by the CYP3A4 enzyme. There are three main metabolic pathways identified: 1) O-demethylation of either side chain or both, followed by oxidation to the carboxylic acids; 2) oxidation of the acetylene moiety followed by hydrolysis to the aryl carboxylic acid; and 3) aromatic hydroxylation of the phenyl-acetylene moiety. The primary metabolites of erlotinib produced by O-demethylation of either side chain have comparable potency to erlotinib in preclinical in vitro assays and in vivo tumour models. They are present in plasma at levels that are < 10% of erlotinib and display similar pharmacokinetics as erlotinib.

Elimination
The metabolites and trace amounts of erlotinib are excreted predominantly via the faeces (> 90%), with renal elimination accounting for only a small amount of an oral dose.

Clearance
A population pharmacokinetic analysis in 591 patients receiving single agent Erlotinib showed a mean apparent clearance of 4.47 L/hour with a median half-life of 36.2 hours. Therefore, the time to reach steady state plasma concentration would be expected to occur in approximately 7 - 8 days.

Patient factors, which correlate with erlotinib pharmacokinetics, are serum total bilirubin, AAG concentrations and current smoking. Elevated serum concentrations of total bilirubin and AAG were associated with a slower rate of erlotinib clearance, however total bilirubin did not exceed normal clinical limits. Smokers had a higher rate of erlotinib clearance.

INDICATIONS
Erlotinib is indicated for-

- the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have previously received chemotherapy.
- the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.

Dosage and administration

STANDARD DOSAGE
Non-small cell lung cancer (NSCLC)
The recommended daily dose of Erlotinib is 150 mg taken on an empty stomach at least one hour before or two hours after the ingestion of food.

Pancreatic Cancer
The recommended daily dose of Erlotinib is 100 mg taken on an empty stomach at least one hour before or two hours after the ingestion of food.

Special Dosage Instructions
Concomitant use of CYP 3A4 substrates and modulators may require dose adjustment.

When dose adjustment is necessary, it is recommended to reduce in 50 mg steps.

Hepatic impairment: Caution should be used when administering Erlotinib to patients with hepatic impairment. Dose interruption or discontinuation is recommended if changes in liver function are severe.

Safety and efficacy have not been studied in patients with severe hepatic impairment.

Renal impairment: The safety and efficacy of Erlotinib has not been studied in patients with renal impairment.

Paediatric use: The safety and efficacy of Erlotinib has not been studied in patients under the age of 18 years.

Smokers: Cigarette smoking has been shown to reduce erlotinib exposure by 50 - 60%. The maximum tolerated dose of Erlotinib in NSCLC patients who currently smoke cigarettes was 300 mg. Efficacy and long term safety of a dose higher than the recommended starting doses have not been established in patients who continue to smoke.

Use in Special Populations

Pregnancy
There are no adequate or well controlled studies in pregnant women using Erlotinib. Studies in animals have shown some reproductive toxicity. The potential risk for humans is unknown. Women of childbearing potential must be advised to avoid pregnancy while on Erlotinib. Adequate contraceptive methods should be used during therapy and for at least 2 weeks after completing therapy. Treatment should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the foetus.

Nursing mothers
It is not known whether erlotinib is excreted in human milk. Because of the potential harm to the infant, mothers should be advised against breastfeeding while receiving Erlotinib.

Hepatic impairment
Erlotinib is eliminated by hepatic metabolism and biliary excretion. Erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh score 7 - 9) compared with patients with adequate hepatic function, including patients with primary liver cancer or hepatic metastases. Safety and efficacy have not been studied in patients with severe hepatic impairment. Caution should be used when administering Erlotinib to patients with hepatic impairment and close monitoring of liver function is recommended in such patients. Erlotinib dosing should be interrupted or discontinued if changes in liver function are severe.

CONTRAINDICATIONS
Erlotinib is contraindicated in patients with severe hypersensitivity to erlotinib or to any component of Erlotinib.

PRECAUSIONS

Interstitial lung disease
Cases of interstitial lung disease (ILD)-like events, including fatalities, have been reported uncommonly in patients receiving Erlotinib for treatment of NSCLC or other advanced solid tumours. In the pivotal study BR.21 in NSCLC, the incidence of serious ILD-like events was 0.8% in each of the placebo and Erlotinib arms. The overall incidence in patients treated with Erlotinib from all studies (including uncontrolled studies and studies with concurrent chemotherapy) is approximately 0.6%. Some examples of reported diagnoses in patients suspected of having ILD-like events include pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome, lung infiltration and alveolitis. These ILD-like events started from a few days to several months after initiating Erlotinib therapy. Most of the cases were associated with confounding or contributing factors such as concomitant or prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease or pulmonary infections.

In patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms, such as dyspnoea, cough and fever, Erlotinib therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, Erlotinib should be discontinued and appropriate treatment initiated as necessary.

Diarrhoea, dehydration, electrolyte imbalance and renal failure
Diarrhoea has occurred in patients on Erlotinib and moderate or severe diarrhoea should be treated with loperamide. In some cases, dose reduction may be necessary. In the event of severe or persistent diarrhoea, nausea, anorexia or vomiting associated with dehydration, Erlotinib therapy should be interrupted and appropriate measures should be taken to treat the dehydration .

There have been rare reports of hypokalaemia and renal failure (including fatalities). Some reports of renal failure were secondary to severe dehydration due to diarrhoea, vomiting and/or anorexia while others were confounded by concomitant chemotherapy. In more severe or persistent cases of diarrhoea, or cases leading to dehydration, particularly in groups of patients with aggravating risk factors (concomitant medications, symptoms or diseases or other predisposing conditions including advanced age), Erlotinib therapy should be interrupted and appropriate measures should be taken to intensively rehydrate the patients intravenously. In addition, renal function and serum electrolytes including potassium should be monitored in patients at risk of dehydration.

Hepatitis, hepatic failure
Rare cases of hepatic failure (including fatalities) have been reported during use of Erlotinib. Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medications. Close monitoring of liver function is therefore recommended in such patients. Erlotinib dosing should be interrupted or discontinued if changes in liver function are severe such as a doubling of total bilirubin and/or a tripling of transaminases relative to pre-treatment levels.

Gastrointestinal perforation
Patients receiving Erlotinib are at increased risk of developing gastrointestinal perforation, which was observed uncommonly (including some cases with a fatal outcome). Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs and/or taxane based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at increased risk. Erlotinib should be permanently discontinued in patients who develop gastrointestinal perforation

ADVERSE EFFECTS
Nausea, vomiting, loss of appetite, mouth sores, dry skin, or eye irritation may occur. Changes in diet such as eating several small meals or limiting activity may help lessen the chance of nausea. If any of these effects persist or worsen, notify your doctor or pharmacist promptly.

Remember that your doctor has prescribed this medication because he or she has judged that the benefit to you is greater than the risk of side effects. Many people using this medication do not have serious side effects.

Diarrhea is a common side effect. Drink plenty of fluids as directed by your doctor to reduce your risk of losing too much body water. Your doctor may prescribe anti-diarrhea medication (e.g., loperamide) to control your symptoms. Tell your doctor immediately if you develop: severe or persistent diarrhea, signs of dehydration (e.g., dizziness, decreased amount of urine).

Tell your doctor immediately if any of these rare but very serious side effects occur: black stools, vomit that looks like coffee grounds, easy bleeding/bruising, stomach/abdominal pain, yellowing eyes or skin, dark urine, unusual fatigue, signs of infection (e.g., fever, chills, persistent sore throat).

Seek immediate medical attention if you develop any of these rare but very serious side effects: new or worsening shortness of breath or cough.

A very serious allergic reaction to this drug is unlikely, but seek immediate medical attention if it occurs. Symptoms of a serious allergic reaction may include: rash, itching, swelling, severe dizziness, trouble breathing.

Erlotinib can commonly cause a mild rash that is usually not serious. However, you may not be able to tell it apart from a rare rash that could be a sign of a severe allergic reaction. Therefore, seek immediate medical attention if you develop any rash.

DRUG INTERACTIONS
Erlotinib is metabolized predominantly by CYP3A4, and inhibitors of CYP3A4 would be expected to increase exposure.

PHARMACEUTICAL INFORMATION

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

Packaging
Erlonix 100 Tablet : Each commercial box contains 30 tablets in Alu-Alu blister pack.

Erlonix 150 Tablet : Each commercial box contains 30 tablets in Alu-Alu blister pack.

Manufactured By
BEACON Pharmaceuticals Limited
Mymensingh, Bangladesh

LF07601