Erlotinib 100/150mg tablets
ERLOCIP

COMPOSITION
ERLOCIP 100
Each film coated tablet contains
Erlotinib ……....100mg

ERLOCIP 150
Each film coated tablet contains
Erlotinib ……....150mg

DOSAGE FORM
Oral tablets

PHARMACOLOGY
Mechanism of Action and Pharmacodynamics
The mechanism of clinical antitumor action of erlotinib is not fully characterized. Erlotinib inhibits the intracellular phosphorylation of tyrosine kinase associated with the epidermal growth factor receptor (EGFR). Specificity of inhibition with regard to other tyrosine kinase receptors has not been fully characterized. EGFR is expressed on the cell surface of normal cells and cancer cells.

Pharmacokinetics
Erlotinib is about 60% absorbed after oral administration and its bioavailability is substantially increased by food to almost 100%. Its half-life is about 36 hours and it is cleared predominantly by CYP3A4 metabolism and to a lesser extent by CYP1A2.

Absorption and Distribution
Bioavailability of erlotinib following a 150 mg oral dose of Erlotinib is about 60% and peak plasma levels occur 4 hrs after dosing. Food increases bioavailability substantially, to almost 100%.

Following absorption, erlotinib is approximately 93% protein bound to albumin and alpha-1 acid glycoprotein (AAG). Erlotinib has an apparent volume of distribution of 232 liters.

Metabolism and Elimination
In vitro assays of cytochrome P450 metabolism showed that erlotinib is metabolized primarily by CYP3A4 and to a lesser extent by CYP1A2, and the extrahepatic isoform CYP1A1. Following a 100 mg oral dose, 91% of the dose was recovered: 83% in feces (1% of the dose as intact parent) and 8% in urine (0.3% of the dose as intact parent).

A population pharmacokinetic analysis in 591 patients receiving single-agent Erlotinib showed a median half-life of 36.2 hours. Time to reach steady state plasma concentration would therefore be 7 – 8 days. No significant relationships of clearance to covariates of patient age, body weight or gender were observed. Smokers had a 24% higher rate of erlotinib clearance.

A second population pharmacokinetic analysis was conducted that incorporated erlotinib data from 204 pancreatic cancer patients who received erlotinib plus gemcitabine. This analysis demonstrated that covariates affecting erlotinib clearance in patients from the pancreatic study were very similar to those seen in the prior single-agent pharmacokinetic analysis. No new covariate effects were identified. Co-administration of gemcitabine had no effect on erlotinib plasma clearance.

Special Populations

Patients with Hepatic Impairment

Erlotinib is cleared predominantly by the liver. No data are currently available regarding the influence of hepatic dysfunction and/or hepatic metastases on the pharmacokinetics of erlotinib.

Patients with Renal Impairment

Less than 9% of a single dose is excreted in the urine. No clinical studies have been conducted in patients with compromised renal function.

Interactions

Erlotinib is metabolized predominantly by CYP3A4, and inhibitors of CYP3A4 would be expected to increase exposure. Co-treatment with the potent CYP3A4 inhibitor ketoconazole increased erlotinib AUC by 2/3.

Pretreatment with the CYP3A4 inducer rifampicin for 7 days prior to Erlotinib administration increased erlotinib clearance by 3-fold and reduced AUC by 2/3. In a separate study, treatment with rifampicin for 11 days, with coadministration of a single 450 mg dose of Erlotinib on day 8 resulted in a mean erlotinib exposure (AUC) that was 57.6% of that observed following a single 150 mg Erlotinib dose in the absence of rifampicin treatment.

Pretreatment and coadministration of Erlotinib decreased the AUC of CYP3A4 substrate, midazolam, by 24%. The mechanism is not clear.

In a Phase Ib study, there were no significant effects of gemcitabine on the pharmacokinetics of erlotinib nor were there significant effects of erlotinib on the pharmacokinetics of gemcitabine.

In the pivotal Phase III NSCLC trial, current smokers achieved erlotinib trough plasma concentrations that were approximately 2-fold less than the former smokers or patients who had never smoked. This effect was accompanied by a

24% increase in apparent erlotinib plasma clearance. When the single dose pharmacokinetics of erlotinib were evaluated in healthy volunteers, current smokers cleared the drug significantly faster than former smoker or volunteers who had never smoked. The AUC_0-infinity in smokers is about 1/3 of that in never/former smokers. This reduced exposure in current smokers is presumably due to induction of CYP1A1 in lung and CYP1A2 in the liver.

INDICATIONS

Non-Small Cell Lung Cancer

Erlotinib monotherapy is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.

Results from two, multicenter, placebo-controlled, randomized, Phase 3 trials conducted in first-line patients with locally advanced or metastatic NSCLC showed no clinical benefit with the concurrent administration of Erlotinib with platinum-based chemotherapy [carboplatin and paclitaxel or gemcitabine and cisplatin] and its use is not recommended in that setting.

Pancreatic Cancer

Erlotinib in combination with gemcitabine is indicated for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.

DOSAGE AND ADMINISTRATION

Non-Small Cell Lung Cancer

The recommended daily dose of Erlotinib is 150 mg taken at least one hour before or two hours after the ingestion of food. Treatment should continue until disease progression or unacceptable toxicity occurs. There is no evidence that treatment beyond progression is beneficial.

Pancreatic Cancer

The recommended daily dose of Erlotinib is 100 mg taken at least one hour before or two hours after the ingestion of food, in combination with gemcitabine (see the gemcitabine package insert). Treatment should continue until disease progression or unacceptable toxicity occurs.

Dose Modifications

In patients who develop an acute onset of new or progressive pulmonary symptoms, such as dyspnea, cough or fever, treatment with Erlotinib should be interrupted pending diagnostic evaluation. If ILD is diagnosed, Erlotinib should be discontinued and appropriate treatment instituted as necessary.

Diarrhea can usually be managed with loperamide. Patients with severe diarrhea who are unresponsive to loperamide or who become dehydrated may require dose reduction or temporary interruption of therapy. Patients with severe skin reactions may also require dose reduction or temporary interruption of therapy.

When dose reduction is necessary, the Erlotinib dose should be reduced in 50 mg decrements.

In patients who are taking Erlotinib with a strong CYP3A4 inhibitor such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), voriconazole, and grapefruit or grapefruit juice, a dose reduction should be considered if severe adverse reactions occur.

Pre-treatment with the CYP3A4 inducer rifampicin decreased erlotinib AUC by about 2/3 to 4/5. Use of alternative treatments lacking CYP3A4 inducing activity is strongly recommended. If an alternative treatment is unavailable, an increase in the dose of Erlotinib should be considered as tolerated at two week intervals while monitoring the patient's safety. The maximum dose of Erlotinib studied in combination with rifampicin is 450 mg. If the Erlotinib dose is adjusted upward, the dose will need to be reduced immediately to the indicated starting dose upon discontinuation of rifampicin or other inducers. Other CYP3A4 inducers include, but are not limited to rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital and St. John's Wort. These too should be avoided if possible.

Erlotinib is eliminated by hepatic metabolism and biliary excretion. Therefore, caution should be used when administering erlotinib to patients with hepatic impairment. Dose reduction or interruption of erlotinib should be considered if severe adverse reactions occur.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Drug interactions

Co-treatment with the potent CYP3A4 inhibitor ketoconazole increases erlotinib AUC by 2/3. Caution should be used when administering or taking Erlotinib with ketoconazole and other strong CYP3A4 inhibitors such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), voriconazole and grapefruit or grapefruit juice.

Pre-treatment with the CYP3A4 inducer rifampicin decreased erlotinib AUC by about 2/3 to 4/5, which is equivalent to a dose of about 30 to 50 mg in NSCLC patients. Use of alternative treatments lacking CYP3A4 inducing activity is strongly recommended. If an alternative treatment is unavailable, adjusting the starting dose should be considered. If the erlotinib dose is adjusted upward, the dose will need to be reduced immediately to the indicated starting dose upon discontinuation of rifampicin or other inducers. Other CYP3A4 inducers include,

but are not limited to, rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital and St. John's Wort.

Pulmonary Toxicity
There have been infrequent reports of serious Interstitial Lung Disease (ILD)-like events, including fatalities, in patients receiving Erlotinib for treatment of NSCLC, pancreatic cancer or other advanced solid tumors. In the randomized single-agent NSCLC study, the incidence of ILD-like events (0.8%) was the same in both the placebo and Erlotinib groups. In the pancreatic cancer study - in combination with gemcitabine -the incidence of ILD-like events was 2.5% in the Erlotinib plus gemcitabine group vs. 0.4% in the placebo plus gemcitabine group.

The overall incidence of ILD-like events in approximately 4900 Erlotinib -treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) was approximately 0.7%. Reported diagnoses in patients suspected of having ILD-like events included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome and lung infiltration. Symptoms started from 5 days to more than 9 months (median 39 days) after initiating Erlotinib therapy. In the lung cancer trials most of the cases were associated with confounding or contributing factors such as concomitant/prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections.

In the event of an acute onset of new or progressive, unexplained pulmonary symptoms such as dyspnea, cough, and fever, Erlotinib therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, Erlotinib should be discontinued and appropriate treatment instituted as needed.

Myocardial infarction/ischemia:
In the pancreatic carcinoma trial, six patients (incidence of 2.3%) in the Erlotinib /gemcitabine group developed myocardial infarction/ischemia. One of these patients died due to myocardial infarction. In comparison, 3 patients in the placebo/gemcitabine group developed myocardial infarction (incidence 1.2%) and one died due to myocardial infarction.

Cerebrovascular accident:
In the pancreatic carcinoma trial, six patients in the Erlotinib /gemcitabine group developed cerebrovascular accidents (incidence: 2.3%) One of these was hemorrhagic and was the only fatal event. In comparison, in the placebo/gemcitabine group there were no cerebrovascular accidents.

Microangiopathic Hemolytic Anemia with Thrombocytopenia:
In the pancreatic carcinoma trial, two patients in the Erlotinib /gemcitabine group developed microangiopathic hemolytic anemia with thrombocytopenia (incidence: 0.8%). Both patients received Erlotinib and gemcitabine concurrently. In

comparison, in the placebo/gemcitabine group there were no cases of microangiopathic hemolytic anemia with thrombocytopenia.

Elevated International Normalized Ratio and Potential Bleeding
International Normalized Ratio (INR) elevations and infrequent reports of bleeding events including gastrointestinal and non-gastrointestinal bleedings have been reported in clinical studies, some associated with concomitant warfarin administration. Patients taking warfarin or other coumarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR.

Hepatotoxicity
Asymptomatic increases in liver transaminases have been observed in Erlotinib treated patients. Rare cases of hepatic failure (including fatalities) have been reported during post-marketing use of Erlotinib. Confounding factors for severe hepatic dysfunction have included pre-existing liver dysfunction from cirrhosis, viral hepatitis, hepatocellular carcinoma, hepatic metastases, or concomitant treatment with potentially hepatotoxic drugs. Therefore, periodic liver function testing (transaminases, bilirubin, and alkaline phosphatase) is recommended. Erlotinib dosing should be interrupted if changes in liver function are severe.

Renal impairment
Cases of acute renal failure or renal insufficiency (including fatalities) with or without hypokalemia have been reported. Some were secondary to severe dehydration due to diarrhea, vomiting, and/or anorexia while others were confounded by concurrent chemotherapy use. In the event of dehydration, particularly in patients with contributing risk factors for renal failure (eg, pre-existing renal disease, medical conditions or medications that may lead to renal disease, or other predisposing conditions including advanced age), Erlotinib therapy should be interrupted and appropriate measures should be taken to intensively rehydrate the patient. Periodic monitoring of renal function and serum electrolytes is recommended in patients at risk of dehydration.

Hepatic Impairment
In vitro and *in vivo* evidence suggest that erlotinib is cleared primarily by the liver. Therefore, erlotinib exposure may be increased in patients with hepatic dysfunction.

Pregnancy
Category D
Erlotinib has been shown to cause maternal toxicity with associated embryo/fetal lethality and abortion in rabbits when given at doses that result in plasma drug concentrations of approximately 3 times those in humans (AUCs at 150 mg daily dose). When given during the period of organogenesis to achieve plasma drug concentrations approximately equal to those in humans, based on AUC, there was no increased incidence of embryo/fetal lethality or abortion in rabbits or rats.

However, female rats treated with 30 mg/m^2/day or 60 mg/m^2/day (0.3 or 0.7 times the clinical dose, on a mg/m^2 basis) of erlotinib prior to mating through the first week of pregnancy had an increase in early resorptions that resulted in a decrease in the number of live fetuses.

No teratogenic effects were observed in rabbits or rats.

There are no adequate and well-controlled studies in pregnant women using Erlotinib. Women of childbearing potential should 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 fetus. If Erlotinib is used during pregnancy, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

Lactation
It is not known whether erlotinib is excreted in human milk. Because many drugs are excreted in human milk and because the effects of Erlotinib on infants have not been studied, women should be advised against breast-feeding while receiving Erlotinib therapy.

Pediatric Use
The safety and effectiveness of Erlotinib in pediatric patients have not been studied.

Geriatric Use
Of the total number of patients participating in the randomized NSCLC trial, 62% were less than 65 years of age, and 38% of patients were aged 65 years or older. The survival benefit was maintained across both age groups. In the pancreatic cancer study, 53% of patients were younger than 65 years of age and 47% were 65 years of age or older. No meaningful differences in safety or pharmacokinetics were observed between younger and older patients in either study. Therefore, no dosage adjustments are recommended in elderly patients.

UNDESIRABLE EFFECTS
Safety evaluation of Erlotinib is based on 856 cancer patients who received Erlotinib as monotherapy, 308 patients who received Erlotinib 100 or 150 mg plus gemcitabine, and 1228 patients who received Erlotinib concurrently with other chemotherapies.

There have been reports of serious events, including fatalities, in patients receiving Erlotinib for treatment of NSCLC, pancreatic cancer or other advanced solid tumors.

Non-Small Cell Lung Cancer

Adverse events, regardless of causality, that occurred in at least 10% of patients treated with single-agent Erlotinib at 150 mg and at least 3% more often than in the placebo group in the randomized trial of patients with NSCLC are summarized by NCI-CTC (version 2.0) Grade in Table 1.

The most common adverse reactions in patients receiving single-agent Erlotinib 150 mg were rash and diarrhea. Grade 3/4 rash and diarrhea occurred in 9% and 6%, respectively, in Erlotinib -treated patients. Rash and diarrhea each resulted in study discontinuation in 1% of Erlotinib -treated patients. Six percent and 1% of patients needed dose reduction for rash and diarrhea, respectively. The median time to onset of rash was 8 days, and the median time to onset of diarrhea was 12 days.

Table 1: Adverse Events Occurring More Frequently (≥ 3%) in the Single Agent Erlotinib Group than in the Placebo Group and in ≥10% of Patients in the Erlotinib Group

	Erlotinib 150 mg N = 485			**Placebo N = 242**		
NCI CTC Grade	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
MedDRA Preferred Term	**%**	**%**	**%**	**%**	**%**	**%**
Rash	75	8	<1	17	0	0
Diarrhea	54	6	<1	18	<1	0
Anorexia	52	8	1	38	5	<1
Fatigue	52	14	4	45	16	4
Dyspnea	41	17	11	35	15	11
Cough	33	4	0	29	2	0
Nausea	33	3	0	24	2	0
Infection	24	4	0	15	2	0
Vomiting	23	2	<1	19	2	0
Stomatitis	17	<1	0	3	0	0
Pruritus	13	<1	0	5	0	0
Dry skin	12	0	0	4	0	0
Conjunctivitis	12	<1	0	2	<1	0
Keratoconjunctivitis sicca	12	0	0	3	0	0
Abdominal pain	11	2	<1	7	1	<1

Liver function test abnormalities (including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin) were observed in patients receiving single-agent Erlotinib 150 mg. These elevations were mainly transient or associated with liver metastases. Grade 2 (>2.5 – 5.0 x ULN) ALT elevations occurred in 4% and <1% of Erlotinib and placebo treated patients, respectively. Grade 3 (>5.0 – 20.0 x ULN) elevations were not observed in Erlotinib -treated

patients. Erlotinib dosing should be interrupted if changes in liver function are severe.

Pancreatic Cancer
Adverse events, regardless of causality, that occurred in at least 10% of patients treated with Erlotinib 100 mg plus gemcitabine in the randomized trial of patients with pancreatic cancer are summarized by NCI-CTC (version 2.0) Grade in Table 2.

The most common adverse reactions in pancreatic cancer patients receiving Erlotinib 100 mg plus gemcitabine were fatigue, rash, nausea, anorexia and diarrhea. In the Erlotinib plus gemcitabine arm, Grade 3/4 rash and diarrhea were each reported in 5% of Erlotinib plus gemcitabine-treated patients. The median time to onset of rash and diarrhea was 10 days and 15 days, respectively. Rash and diarrhea each resulted in dose reductions in 2% of patients, and resulted in study discontinuation in up to 1% of patients receiving Erlotinib plus gemcitabine. The 150 mg cohort was associated with a higher rate of certain class-specific adverse reactions including rash and required more frequent dose reduction or interruption.

Table 2: Adverse Events Occurring in ≥10% of Erlotinib -treated Pancreatic Cancer Patients: 100 mg cohort

	Erlotinib + Gemcitabine 1000 mg/m2 IV N=259			**Placebo + Gemcitabine 1000 mg/m2 IV N=256**		
NCI CTC Grade	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
MedDRA Preferred Term	**%**	**%**	**%**	**%**	**%**	**%**
Fatigue	73	14	2	70	13	2
Rash	69	5	0	30	1	0
Nausea	60	7	0	58	7	0
Anorexia	52	6	<1	52	5	<1
Diarrhea	48	5	<1	36	2	0
Abdominal pain	46	9	<1	45	12	<1
Vomiting	42	7	<1	41	4	<1
Weight decreased	39	2	0	29	<1	0
Infection*	39	13	3	30	9	2
Edema	37	3	<1	36	2	<1
Pyrexia	36	3	0	30	4	0
Constipation	31	3	1	34	5	1
Bone pain	25	4	<1	23	2	0
Dyspnea	24	5	<1	23	5	0
Stomatitis	22	<1	0	12	0	0
Myalgia	21	1	0	20	<1	0

Depression	19	2	0	14	<1	0
Dyspepsia	17	<1	0	13	<1	0
Cough	16	0	0	11	0	0
Dizziness	15	<1	0	13	0	<1
Headache	15	<1	0	10	0	0
Insomnia	15	<1	0	16	<1	0
Alopecia	14	0	0	11	0	0
Anxiety	13	1	0	11	<1	0
Neuropathy	13	1	<1	10	<1	0
Flatulence	13	0	0	9	<1	0
Rigors	12	0	0	9	0	0

* Includes all MedDRA preferred terms in the Infections and Infestations System Organ Class

In the pancreatic carcinoma trial, 10 patients in the Erlotinib plus gemcitabine group developed deep venous thrombosis (incidence: 3.9%). In comparison, 3 patients in the placebo plus gemcitabine group developed deep venous thrombosis (incidence 1.2%). The overall incidence of Grade 3 or 4 thrombotic events, including deep venous thrombosis, was similar in the two treatment arms: 11% for Erlotinib plus gemcitabine and 9% for placebo plus gemcitabine.

No differences in Grade 3 or Grade 4 hematologic laboratory toxicities were detected between the Erlotinib plus gemcitabine group compared to the placebo plus gemcitabine group.

Severe adverse events (≥ Grade 3 NCI CTC) in the Erlotinib plus gemcitabine group with incidences < 5% included syncope, arrhythmias, ileus, pancreatitis, hemolytic anemia including microangiopathic hemolytic anemia with thrombocytopenia, myocardial infarction/ischemia, cerebrovascular accidents including cerebral hemorrhage, and renal insufficiency.

Liver function test abnormalities (including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin) have been observed following the administration of Erlotinib plus gemcitabine in patients with pancreatic cancer. Table 3 displays the most severe NCI-CTC Grade of liver function abnormalities that developed. Erlotinib dosing should be interrupted if changes in liver function are severe.

Table 3: Liver Function Test Abnormalities (most severe NCI-CTC Grade) in Pancreatic Cancer Patients: 100 mg Cohort						
	Erlotinib + Gemcitabine 1000mg/m2 IV N = 259			**Placebo + Gemcitabine 1000 mg/m2 IV N = 256**		
NCI CTC Grade	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 2**	**Grade 3**	**Grade 4**
Bilirubin	17 %	10%	<1%	11%	10%	3%
ALT	31%	13%	<1%	22%	9%	0%
AST	24%	10%	<1%	19%	9%	0%

NSCLC and Pancreatic Cancer Indications
During the NSCLC and the combination pancreatic cancer trials, infrequent cases of gastrointestinal bleeding have been reported, some associated with concomitant warfarin or NSAID administration. These adverse events were reported as peptic ulcer bleeding (gastritis, gastroduodenal ulcers), hematemesis, hematochezia, melena and hemorrhage from possible colitis. Cases of acute renal failure or renal insufficiency, including fatalities, with or without hypokalemia have been reported. Cases of Grade 1 epistaxis were also reported in both the single-agent NSCLC and the pancreatic cancer clinical trials.

NCI-CTC Grade 3 conjunctivitis and keratitis have been reported infrequently in patients receiving Erlotinib therapy in the NSCLC and pancreatic cancer clinical trials. Corneal ulcerations may also occur.

Hepatic failure has been reported in patients treated with single-agent ERLOTINIB or Erlotinib combined with chemotherapy in clinical studies and during post-marketing use of Erlotinib; it is not possible to reliably estimate the frequency or establish a causal relationship to Erlotinib treatment. In general, no notable differences in the safety of Erlotinib monotherapy or in combination with gemcitabine could be discerned between females or males and between patients younger or older than the age of 65 years. The safety of Erlotinib appears similar in Caucasian and Asian patients.

OVERDOSAGE
Single oral doses of Erlotinib up to 1,000 mg in healthy subjects and weekly doses up to 1,600 mg in cancer patients have been tolerated. Repeated twice-daily doses of 200 mg single-agent Erlotinib in healthy subjects were poorly tolerated after only a few days of dosing. Based on the data from these studies, an unacceptable incidence of severe adverse events, such as diarrhea, rash, and liver transaminase elevation, may occur above the recommended dose. In case of suspected overdose, Erlotinib should be withheld and symptomatic treatment instituted.

SHELF-LIFE
2 years

STORAGE AND HANDLING INSTRUCTIONS
Store in a cool dry place

PACKAGING INFORMATION
Container pack of 10 and 30 tablets

Last updated: May 2009