260x230 mm

For the use of an Oncologist only

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Erlotinib Tablets IP 100 mg

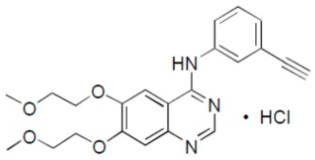
ERLOTERO-100

ऐरलोटेरो-100

GENERIC NAME
Erlotinib Tablets IP 100 mg

COMPOSITION
Each film coated tablet contains:
Erlotinib Hydrochloride IP equivalent to
Erlotinib 100 mg.
Excipients q.s.
Colour : Titanium Dioxide IP

DESCRIPTION
Erlotinib a kinase inhibitor, is a quinazolinamine with the chemical name N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)4-quinazolinamine. Erlotinib hydrochloride has the molecular formula C22H23N3O4.HCl and a molecular weight of 429.90. Erlotinib contains erlotinib as the hydrochloride salt that has the following structural formula:



Erlotinib hydrochloride is very slightly soluble in water, slightly soluble in methanol and practically insoluble in acetonitrile, acetone, ethyl acetate and hexane.

DOSAGE FORM
Tablets

INDICATION
Erlotinib is indicated:

for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen
In combination with gemcitabine for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.

DOSAGE AND ADMINISTRATION
The recommended daily dose of erlotinib for NSCLC 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.
The recommended daily dose of Erlotinib for pancreatic cancer is 100 mg taken in combination with gemcitabine at least one hour before or two hours after the ingestion of food.

USE IN SPECIAL POPULATION
Pregnancy
Based on its mechanism of action, erlotinib can cause fetal harm when administered to a pregnant woman. When given during organogenesis, erlotinib administration resulted in embryo-fetal lethality and abortion in rabbits at doses approximately 3 times the recommended human daily dose of 150 mg. If erlotinib is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.
Nursing Mothers
It is not known whether erlotinib is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from erlotinib, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use
The safety and effectiveness of Erlotinib in pediatric patients have not been established.
Geriatric Use
Of the 1297 subjects in clinical studies of Erlotinib for the treatment of NSCLC and pancreatic cancer 40% were 65 and older while 10% were 75 and older. No overall differences in safety or efficacy were observed between subjects 65 years and older and those younger than 65.
Females and Males of Reproductive Potential
Contraception
Females
Counsel patients on pregnancy planning and prevention. Advise female patients of reproductive potential to use highly effective contraception during treatment with erlotinib, and for at least 2 weeks after the last dose of erlotinib. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking erlotinib.
Patients with Hepatic Impairment
Patients with hepatic impairment (total bilirubin > upper limit of normal (ULN) or Child-Pugh A, B and C) should be closely monitored during therapy with erlotinib. Treatment with erlotinib should be used with extra caution in patients with total bilirubin > 3 x ULN.
In vitro and in *vivo* evidence suggest that erlotinib is cleared primarily by the liver. However, erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh B) compared with patients with adequate hepatic function including patients with primary liver cancer or hepatic metastases.
Patients with Renal Impairment
The safety and efficacy of erlotinib has not been studied in patients with renal impairment (serum creatinine concentration >1.5 times the upper normal limit). Based on pharmacokinetic data no dose adjustments appear necessary in patients with mild or moderate renal impairment. Use of Erlotinib in patients with severe renal impairment is not recommended.
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 cigarettes. Therefore, current smokers should be advised to stop smoking, as plasma concentrations of Erlotinib in smokers as compared to non-smokers are reduced.

CONTRAINDICATIONS
Hypersensitivity to Erlotinib or to any of the excipients of product

WARNINGS AND PRECAUTIONS
Interstitial Lung Disease (ILD)
Cases of serious ILD, including fatal cases, can occur with erlotinib treatment. The overall incidence of ILD in approximately 32,000 erlotinib-treated patients in uncontrolled studies and studies with concurrent chemotherapy was approximately 1.1%. In patients with ILD, the onset of symptoms was between 5 days to more than 9 months (median 39 days) after initiating erlotinib therapy.
Withhold erlotinib for acute onset of new or progressive unexplained pulmonary symptoms such as dyspnea, cough, and fever pending diagnostic evaluation. If ILD is confirmed, permanently discontinue erlotinib.
Renal Failure
Hepatorenal syndrome, severe acute renal failure including fatal cases, and renal insufficiency can occur with erlotinib treatment. Renal failure may arise from exacerbation of underlying baseline hepatic impairment or severe dehydration. The pooled incidence of severe renal impairment in the 3 monotherapy lung cancer studies was 0.5% in the erlotinib arms and 0.8% in the control arms. The incidence of renal impairment in the pancreatic cancer study was 1.4% in the erlotinib plus gemcitabine arm and 0.4% in the control arm. Withhold erlotinib in patients developing severe renal impairment until renal toxicity is resolved. Perform periodic monitoring of renal function and serum electrolytes during erlotinib treatment.
Hepatotoxicity with or without Hepatic Impairment
Hepatic failure and hepatorenal syndrome, including fatal cases, can occur with erlotinib treatment in patients with normal hepatic function; the risk of hepatic toxicity is increased in patients with baseline hepatic impairment. In clinical studies where patients with moderate to severe hepatic impairment were excluded, the pooled incidence of hepatic failure in the 3 monotherapy lung cancer studies was 0.4% in the erlotinib arms and 0% in the control arms. The incidence of hepatic failure in the pancreatic cancer study was 0.4% in the erlotinib plus gemcitabine arm and 0.4% in the control arm. In a pharmacokinetic study in 15 patients with moderate hepatic impairment (Child-Pugh B) associated with significant liver tumor burden, 10 of these 15 patients died within 30 days of the last erlotinib dose. One patient died from hepatorenal syndrome, 1 patient died from rapidly progressing liver failure and the remaining 8 patients died from progressive disease. Six out of the 10 patients who died had baseline total bilirubin > 3 x ULN.
Perform periodic liver testing (transaminases, bilirubin, and alkaline phosphatase) during treatment with erlotinib. Increased frequency of monitoring of liver function is required for patients with pre-existing hepatic impairment or biliary obstruction. Withhold erlotinib in patients without pre-existing hepatic impairment for total bilirubin levels greater than 3 times the upper limit of normal or transaminases greater than 5 times the upper limit of normal. Withhold erlotinib in patients with pre-existing hepatic impairment or biliary obstruction for doubling of bilirubin or tripling of transaminases values over baseline. Discontinue erlotinib in patients whose abnormal liver tests meeting the above criteria do not improve significantly or resolve within three weeks.
Gastrointestinal Perforation
Gastrointestinal perforation, including fatal cases, can occur with erlotinib treatment. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, or taxane-based chemotherapy, or who have prior history of peptic ulceration or diverticular disease may be at increased risk of perforation. The pooled incidence of gastrointestinal perforation in the 3 monotherapy lung cancer studies was 0.2% in the erlotinib arms and 0.1% in the control arms. The incidence of gastrointestinal perforation in the pancreatic cancer study was 0.4% in the erlotinib plus gemcitabine arm and 0% in the control arm. Permanently discontinue erlotinib in patients who develop gastrointestinal perforation.
Bullous and Exfoliative Skin Disorders
Bullous, blistering and exfoliative skin conditions, including cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal, can occur with erlotinib treatment. The pooled incidence of bullous and exfoliative skin disorders in the 3 monotherapy lung cancer studies was 1.2% in the erlotinib arms and 0% in the control arms. The incidence of bullous and exfoliative skin disorders in the pancreatic cancer study was 0.4% in the erlotinib plus gemcitabine arm and 0% in the control arm. Discontinue erlotinib treatment if the patient develops severe bullous, blistering or exfoliating conditions.
Myocardial Infarction/Ischemia
In the pancreatic carcinoma trial, six patients (incidence of 2.1%) 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 1.1%), and one died due to myocardial infarction. The pooled incidence of myocardial infarction/ischemia in the 3 monotherapy lung cancer studies was 0.2% in the erlotinib arms and 0.4% in the control arms.
Cerebrovascular Accident
In the pancreatic carcinoma trial, seven patients in the erlotinib/gemcitabine group developed cerebrovascular accidents (incidence: 2.5%). One of these was hemorrhagic and was the only fatal event. In comparison, in the placebo/gemcitabine group there were no cerebrovascular accidents. The pooled incidence of cerebrovascular accident in the 3 monotherapy lung cancer studies was 0.6% in the erlotinib arms and 0.9% in the control arms.
Microangiopathic Hemolytic Anemia with Thrombocytopenia
The pooled incidence of microangiopathic hemolytic anemia with thrombocytopenia in the 3 monotherapy lung cancer studies was 0% in the erlotinib arms and 0.1% in the control arms. The incidence of microangiopathic hemolytic anemia with thrombocytopenia in the pancreatic cancer study was 1.4% in the erlotinib plus gemcitabine arm and 0% in the control arm.
Ocular Disorders
Decreased tear production, abnormal eyelash growth, keratoconjunctivitis sicca or keratitis can occur with erlotinib treatment and can lead to corneal perforation or ulceration. The pooled incidence of ocular disorders in the 3 monotherapy lung cancer studies was 17.8% in the erlotinib arms and 4% in the control arms. The incidence of ocular disorders in the pancreatic cancer study was 12.8% in the erlotinib plus gemcitabine arm and 11.4% in the control arm. Interrupt or discontinue erlotinib therapy if patients present with acute or worsening ocular disorders such as eye pain.

Hemorrhage in Patients Taking Warfarin
Severe and fatal hemorrhage associated with International Normalized Ratio (INR) elevations can occur when erlotinib and warfarin are administered concurrently. Regularly monitor prothrombin time and INR during erlotinib treatment in patients taking warfarin or other coumarin-derivative anticoagulants.
Embryo-Fetal Toxicity
Based on its mechanism of action, erlotinib can cause fetal harm when administered to a pregnant woman. When given during organogenesis, erlotinib administration resulted in embryo-fetal lethality and abortion in rabbits at doses approximately 3 times the recommended human daily dose of 150 mg. If erlotinib is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.
Advise females of reproductive potential to use highly effective contraception during therapy, and for at least 2 weeks after the last dose of erlotinib. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking erlotinib.
Smokers
Current smokers should be advised to stop smoking, as plasma concentrations of erlotinib in smokers as compared to non-smokers are reduced. The degree of reduction is likely to be clinically significant.

DRUG INTERACTIONS
CYP3A4 Inhibitors
Erlotinib is metabolized predominantly by CYP3A4. Co-treatment with the potent CYP3A4 inhibitor ketoconazole increased erlotinib AUC by 67%. When ERLOTINIB was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2, the erlotinib exposure [AUC] and maximum concentration [Cmax] increased by 39% and 17%, respectively. Dose modifications are recommended.
CYP3A4 Inducers
Pre-treatment with the CYP3A4 inducer rifampicin for 7-11 days prior to erlotinibdecreased erlotinib AUC by 58% to 80%. Dose modifications are recommended.
Drugs Affecting Gastric pH
Co-administration of erlotinib with omeprazole decreased erlotinib AUC by 46% and co-administration of erlotinib with ranitidine 300 mg decreased erlotinib AUC by 33%. When erlotinib was administered with ranitidine 150 mg twice daily (at least 10 h after the previous ranitidine evening dose and 2 h before the ranitidine morning dose), erlotinib AUC decreased by 15%. Increasing the dose of erlotinib when co-administered with such agents is not likely to compensate for the loss of exposure. Scheduling modifications are recommended.
Cigarette Smoking
Cigarette smoking results in reductions in erlotinib AUC. Dose modifications are recommended.
Anticoagulants
Interaction with coumarin-derived anticoagulants, including warfarin, leading to increased International Normalized Ratio (INR) and bleeding adverse reactions, which in some cases were fatal, have been reported in patients receiving erlotinib. Regularly monitor prothrombin time or INR in patients taking coumarin-derived anticoagulants. Dose modifications of erlotinib are not recommended.
Statins
The combination of Erlotinib and a statin may increase the potential for statin-induced myopathy, including rhabdomyolysis, which was observed rarely.
Erlotinib and P-glycoprotein inhibitors
Erlotinib is a substrate for the P-glycoprotein active substance transporter. Concomitant administration of inhibitors of Pgp, e.g. cyclosporine and verapamil, may lead to altered distribution and/or altered elimination of erlotinib. The consequences of this interaction for e.g. CNS toxicity have not been established. Caution should be exercised in such situations.
Erlotinib and proteasome inhibitors
Due to the working mechanism, proteasome inhibitors including bortezomib may be expected to influence the effect of EGFR inhibitors including erlotinib. Such influence is supported by limited clinical data and preclinical studies showing EGFR degradation through the proteasome.

ADVERSE EFFECTS
Non-small cell lung cancer (Erlotinib administered as monotherapy)
In a randomized double-blind study (BR.21; erlotinib administered as second line therapy), rash (75%) and diarrhoea (54%) were the most commonly reported adverse drug reactions (ADRs). Most were Grade 1/2 in severity and manageable without intervention. Grade 3/4 rash and diarrhoea occurred in 9% and 6%, respectively in erlotinib-treated patients and each resulted in study discontinuation in 1% of patients. Dose reduction for rash and diarrhoea was needed in 6% and 1% of patients, respectively. In study BR.21, the median time to onset of rash was 8 days, and the median time to onset of diarrhoea was 12 days.
The following terms are used to rank the undesirable effects by frequency: 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) including isolated reports.
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

HETERO HEALTHCARE LIMITED		Packaging Development	
Customer/Market	HHL	Layout No.	NA
Substract	60 ± 15% Gsm Maplitho paper with 3 vertical & 2 horizontal fold at equal distance, printed product insert 260x230 mm		
Material code	12001574-00	Artwork code	12001574-00
Reason for change	New artwork		
Pantone No/ CMYK %	Black		

260x230 mm

Table 1: Very common ADRs in study BR.21

	Erlotinib N = 485			Placebo N = 242		
NCI-CTC Grade	**Any Grade**	3	4	**Any Grade**	3	4
MedDRA Preferred Term	**%**	**%**	**%**	**%**	**%**	**%**
Total patients with any AE	99	40	22	96	36	22
Infections and infestations Infection*	24	4	0	15	2	0
Metabolism and nutrition disorders Anorexia	52	8	1	38	5	<1
Eye disorders Keratoconjunctivitis sicca Conjunctivitis	12 12	0 <1	0 0	3 2	0 <1	0 0
Respiratory, thoracic and mediastinal disorders Dyspnoea	41 33	17 4	11 0	35 29	15 2	11 0
Cough						
Gastrointestinal disorders Diarrhoea** Nausea Vomiting Stomatitis Abdominal pain	54 33 23 17 11	6 3 2 <1 2	<1 0 <1 0 <1	18 24 19 3 7	<1 2 2 0 1	0 0 0 0 <1
Skin and subcutaneous tissue disorders Rash*** Pruritus Dry skin	75 13 12	8 <1 0	<1 0 0	17 5 4	0 0 0	0 0 0
General disorders and administration site conditions Fatigue	52	14	4	45	16	4

* Severe infections, with or without neutropenia, have included pneumonia, sepsis, and cellulitis.
** Can lead to dehydration, hypokalemia and renal failure.
*** Rash included dermatitis acneiform.
The most frequent ADRs seen in patients treated with erlotinib in studies BO18192 and BO25460 were rash and diarrhoea (see Table 2). No Grade 4 rash or diarrhoea was observed in either study. Rash and diarrhoea resulted in discontinuation of erlotinib in 1% and <1% of patients, respectively, in study BO18192, while no patients discontinued for rash or diarrhoea in BO25460. Dose modifications (interruptions or reductions) for rash and diarrhoea were needed in 8.3% and 3% of patients, respectively, in study BO18192 and 5.6% and 2.8% of patients, respectively, in study Bo25460.

Table 2: Most frequent ADRs in Studies BO18192 (SATURN) and BO25460 (IUNO)

	BO18192 (SATURN)*		Bo25460 (IUNO)*	
	Erlotinib n=433	**Placebo n=445**	**Erlotinib n=322**	**Placebo n=319**
	%	**%**	**%**	**%**
Rash, all grades	49.2	5.8	39.4	10.0
Grade 3	6.0	0	5.0	1.6
Diarrhoea, all grades	20.3	4.5	24.2	4.4
Grade 3	1.8	0	2.5	0.3

*Safety analysis population
The most frequent ADRs seen in patients treated with Erlotinib in study ML20650 were rash and diarrhoea (any Grade 80% and 57%, respectively), most were Grade 1/2 in severity and manageable without intervention. Grade 3 rash and diarrhoea occurred in 9% and 4% of patients, respectively. No Grade 4 rash or diarrhoea was observed. Both rash and diarrhoea resulted in discontinuation of Erlotinib in 1% of patients. Dose modifications (interruptions or reductions) for rash and diarrhoea were needed in 11% and 7% of patients, respectively.
Pancreatic cancer ((Erlotinib administered concurrently with gemcitabine)
The most common adverse reactions in pivotal study PA.3 in pancreatic cancer patients receiving Erlotinib 100 mg plus gemcitabine were fatigue, rash and diarrhoea.

In the Erlotinib plus gemcitabine arm, Grade 3/4 rash and diarrhoea were each reported in 5% of patients. The median time to onset of rash and diarrhoea was 10 days and 15 days, respectively. Rash and diarrhoea each resulted in dose reductions in 2% of patients, and resulted in study discontinuation in up to 1% of patients receiving Erlotinib plus gemcitabine.
Adverse reactions occurring more frequently (≥3%) in Erlotinib 100 mg plus gemcitabine-treated patients than in the placebo plus gemcitabine group in the pivotal study PA.3, and in at least 10% of patients in the Erlotinib 100 mg plus gemcitabine group, are summarised by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Grade in Table 3.
The following terms are used to rank the undesirable effects by frequency: 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) including isolated reports.
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: Very common ADRs in study PA.3 (100 mg cohort)

	Erlotinib N = 259			Placebo N = 242		
NCI-CTC Grade	Any Grade	3	4	Any Grade	3	4
MedDRA Preferred Term	%	%	%	%	%	%
Total patients with any AE	99	48	22	97	48	16
Infections and infestations Infection*	31	3	<1	24	6	<1
Metabolism and nutrition disorders Weight decreased	39	2	0	29	<1	0
Psychiatric disorders Depression	19	2	0	14	<1	0
Nervous system disorders Neuropathy Headache	13 15	1 <1	<1 0	10 10	<1 0	0 0
Respiratory ,thoracic and mediastinal disorders Cough	16	0	0	11	0	0
Gastrointestinal disorders Diarrhoea** Stomatitis Dyspepsia Flatulence	48 22 17 13	5 <1 <1 0	<1 0 0 0	36 12 13 9	2 0 <1 <1	0 0 0 0
Skin and subcutaneous tissue disorders Rash*** Alopecia	69 14	5 0	0 0	30 11	1 0	0 0
General disorders and administration site conditions Fatigue Pyrexia Rigors	73 36 12	14 3 0	2 0 0	70 30 9	13 4 0	2 0 0

* Severe infections, with or without neutropenia, have included pneumonia, sepsis, and cellulitis.
** Can lead to dehydration, hypokalemia and renal failure.
*** Rash included dermatitis acneiform.
Other Observations:
Safety evaluation of Erlotinib is based on the data from more than 1500 patients treated with at least one 150 mg dose of Erlotinib monotherapy and more than 300 patients who received Erlotinib 100 or 150 mg in combination with gemcitabine.
The following adverse reactions have been observed in patients who received Erlotinib administered as single agent and patients who received Erlotinib concurrently with chemotherapy.
Very common ADRs from the BR 21 and PA 3 studies are presented in Tables 1 and 3, other ADRs including those from other studies are summarized below.
Eye disorders
Common: Keratitis, Conjunctivitis
Uncommon: Eyelash changes
Very rare: Corneal perforations, Corneal ulcerations, Uveitis
Respiratory, thoracic and mediastinal disorders
Common: Epistaxis, Serious interstitial lung disease (ILD)
Gastrointestinal disorders
Very common: Diarrhoea
Common: Gastrointestinal bleeding
Uncommon: Gastrointestinal perforations
Hepato-biliary disorders
Very common: Liver function test abnormalities
Rare: Hepatic failure
Skin and subcutaneous tissue disorders
Common: Alopecia, Dry skin, Paronychia, Folliculitis, Acne/ Dermatitis acneiform, Skin fissures
Uncommon: Hirsutism, Eyebrow changes, Brittle and Loose nails,Mild skin reactions such as hyperpigmentation
Rare: Palmar plantar erythrodys-aesthesia syndrome
Very rare: Stevens-Johnson syndrome/Toxic epidermal necrolysis
Renal and urinary disorders
Common: Renal insufficiency
Uncommon: Nephritis, Proteinuria

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 reactions, 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.

CLINICAL PHARMACOLOGY
Mechanism of action
Erlotinib is an epidermal growth factor receptor/human epidermal growth factor receptor type 1 (EGFR also known as HER1) tyrosine kinase inhibitor. Erlotinib potently inhibits the intracellular phosphorylation of EGFR. EGFR 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.
EGFR mutations may lead to constitutive activation of anti-apoptotic and proliferation signaling pathways. The potent effectiveness of erlotinib in blocking EGFR-mediated signalling in these EGFR mutation positive tumours is attributed to the tight binding of erlotinib to the ATP-binding site in the mutated kinase domain of the EGFR. Due to the blocking of downstream-signaling, the proliferation of cells is stopped, and cell death is induced through the intrinsic apoptotic pathway. Tumour regression is observed in mouse models of enforced expression of these EGFR activating mutations.
Pharmacokinetics
Absorption
After oral administration, erlotinib peak plasma levels are obtained in approximately 4 hours after oral dosing. A study in normal healthy volunteers provided an estimate of the absolute bioavailability of 59%. The exposure after an oral dose may be increased by food.
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 non-small cell lung cancer [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 1185 ng/g of tissue. This corresponded to an overall average of 63% (range 5-161%) of the steady state observed peak plasma concentrations. The primary active metabolites were present in tumour at concentrations averaging 160 ng/g tissue, which corresponded to an overall average of 113% (range 88-130%) of the observed steady state peak plasma concentrations. Plasma protein binding is approximately 95%. Erlotinib binds to serum albumin and alpha-1 acid glycoprotein (AAG).
Biotransformation
Erlotinib is metabolised in the liver by the hepatic cytochromes in humans, primarily CYP3A4 and to a lesser extent by CYP1A2. Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung, and 1B1 in tumour tissue potentially contribute to the metabolic clearance of Erlotinib.
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 OSI-420 and OSI-413 of Erlotinib produced by O-demethylation of either side chain have comparable potency to Erlotinib in non-clinical 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
Erlotinib is excreted predominantly as metabolites via the faeces (>90%) with renal elimination accounting for only a small amount (approximately 9%) of an oral dose. Less than 2% of the orally administered dose is excreted as parent substance. A population pharmacokinetic analysis in 591 patients receiving single agent Erlotinib shows 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.

INCOMPATIBILITIES
Not applicable

STORAGE & HANDLING
Store below 25ºC. Protect from light and moisture.
Keep container tightly closed.
Dispense in original container.
Do not use if seal over bottle opening is broken or missing.
Keep all medicines out of reach of children.

PACKAGING INFORMATION
Bottle containing 30 tablets

Mfg. Lic. No.: 405/DR/mfg/2017

Manufactured in India by:
HETERO HEALTHCARE LIMITED
AIIDC Industrial Growth Centre,
Changsari, Niz Sindurighopa (Village),
Sila Sindurighopa (Mouza),
Kamrup (Dist) Assam – 781101

12001574-00

HETERO HEALTHCARE LIMITED	Packaging Development		
Customer/Market	HHL	Layout No.	NA
Substract	60 ± 15% Gsm Maplitho paper with 3 vertical & 2 horizontal fold at equal distance, printed product insert 260x230 mm		
Material code	12001574-00	Artwork code	12001574-00
Reason for change	New artwork		
Pantone No/ CMYK %	Black		