Prescribing Information
RILTARED 25 (Erlotinib Film-Coated Tablets 25 mg)
RILTARED 100 (Erlotinib Film-Coated Tablets 100 mg)
RILTARED 150 (Erlotinib Film-Coated Tablets 150mg)

COMPOSITION
RILTARED 25 (Erlotinib Film-Coated Tablets 25 mg):
Each Film-Coated Tablet Contains: Erlotinib Hydrochloride 27.3 mg equivalent to Erlotinib 25 mg

RILTARED 100 (Erlotinib Film-Coated Tablets 100 mg):
Each Film-Coated Tablet Contains: Erlotinib Hydrochloride 109.30 mg equivalent to Erlotinib 100 mg

RILTARED 150 (Erlotinib Film-Coated Tablets 150 mg):
Each Film-Coated Tablet Contains: Erlotinib Hydrochloride 163.90 mg equivalent to Erlotinib 150 mg

PHARMACEUTICAL FORM
Film Coated Tablet

RILTARED 25 (Erlotinib Film-Coated Tablets 25 mg): White to off white film coated round tablets with 'E' de-bossed on one side and plain on other side.

RILTARED 100 (Erlotinib Film-Coated Tablets 100 mg): White to off white film coated round tablets with 'E' de-bossed on one side and '100' on other side.

RILTARED 150 (Erlotinib Film-Coated Tablets 150 mg): White to off white film coated round tablets with 'E' de-bossed on one side and '150' on other side.

CLINICAL INFORMATION
Therapeutic indication
Non-small cell lung cancer
Riltared is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR activating mutations.
Riltared is indicated for maintenance treatment in patients with locally advanced or metastatic NSCLC with EGFR activating mutations who have not progressed after firstline chemotherapy.
Riltared is also indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

Pancreatic Cancer
Riltared in combination with gemcitabine is indicated for the treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer

Posology and method of administration
Standard Dosage
Non-small cell lung cancer
EGFR mutation testing should be performed prior to initiation of Riltared as first-line or maintenance therapy in patients with locally advanced or metastatic NSCLC.
The recommended daily dose of Riltared is 150 mg taken at least one hour before or two hours after the ingestion of food.

Pancreatic Cancer
The recommended daily dose of Riltared is 100 mg taken at least one hour before or two hours after the ingestion of food, in combination with gemcitabine (see the package insert of gemcitabine for the pancreatic cancer indication)

Special dosage instructions
Drug Interactions: Concomitant use of CYP 3A4 substrates and modulators may require dose adjustment (see section Interactions with other Medicinal Products and other Forms of Interaction).
When dose adjustment is necessary, it is recommended to reduce in 50 mg steps (see sections Warnings and Precautions and Interactions with other Medicinal Products and other Forms of Interaction).

Hepatic impairment: Erlotinib is eliminated by hepatic metabolism and biliary excretion. Although erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh score 7-9) compared with patients with adequate hepatic function, caution should be used when administering Riltared to patients with hepatic impairment. Dose reduction or interruption of Riltared should be considered if severe adverse reactions occur. Safety and efficacy have not been studied in patients with severe hepatic impairment (see sections Warnings & Precautions [Hepatitis, hepatic failure] and Pharmacokinetics in Special Populations)

Renal impairment: The safety and efficacy of Riltared has not been studied in patients with renal impairment. (see section, Pharmacokinetics in Special Populations).

Pediatric use: The safety and efficacy of Riltared in the approved indications has not been established 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 Riltared in NSCLC patients who currently smoke cigarettes was 300 mg. The 300mg dose did not show improved efficacy in second line treatment after failure of chemotherapy compared to the recommended 150mg dose in patients who continue to smoke cigarettes (see section Interactions with other Medicinal Products and other Forms of Interaction and section Pharmacokinetics in Special Populations).

Route of administration
Oral

Contraindications
Hypersensitivity to erlotinib or to any of the excipients.

Special warnings and precautions for use
Assessment of EGFR mutation status
When considering the use of Riltared as a first line or maintenance treatment for locally advanced or metastatic NSCLC, it is important that the EGFR mutation status of a patient is determined.
A validated, robust, reliable and sensitive test with a prespecified positivity threshold and demonstrated utility for the determination of EGFR mutation status, using either tumor DNA derived from a tissue sample or circulating free DNA (cfDNA) obtained from a blood (plasma) sample, should be performed according to local medical practice.
If a plasma-based cfDNA test is used and the result is negative for activating mutations, perform a tissue test wherever possible due to the potential for false negative results from a plasma-based test.

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.

Interstitial Lung Disease

Cases of interstitial lung disease (ILD)-like events, including fatalities, have been reported uncommonly in patients receiving Erlotinib for treatment of non-small cell lung cancer (NSCLC), pancreatic cancer or other advanced solid tumours. 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 (ARDS), alveolitis, and lung infiltration. Symptoms started from a few days to several months after initiating Erlotinib therapy. Confounding or contributing factors such as concomitant or prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections were frequent. A higher incidence of ILD is seen among patients in Japan.

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. Patients treated concurrently with erlotinib and gemcitabine should be monitored carefully for the possibility to develop ILD-like toxicity. If ILD is diagnosed, Riltared should be discontinued and appropriate treatment initiated as necessary.

Diarrhoea, dehydration, electrolyte imbalance and renal failure

Diarrhoea (including very rare cases with a fatal outcome) has occurred in patients on Erlotinib and moderate or severe diarrhoea should be treated with e.g. loperamide. In some cases dose reduction may be necessary by 50 mg steps. Dose reductions by 25 mg steps have not been investigated. In the event of severe or persistent diarrhoea, nausea, anorexia, or vomiting associated with dehydration, Riltared 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 cases 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 (especially concomitant chemotherapy and other medications, symptoms or diseases or other predisposing conditions including advanced age), Riltared 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. Therefore, in such patients, periodic liver function testing should be considered. Riltared dosing should be interrupted if changes in liver function are severe. Riltared is not recommended for use in patients with severe hepatic dysfunction.

Gastrointestinal perforation

Patients receiving Riltared 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. Riltared should be permanently discontinued in patients who develop gastrointestinal perforation.

Bullous and exfoliative skin disorders

Bullous, blistering and exfoliative skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal. Riltared treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or

exfoliating conditions. Patients with bullous and exfoliative skin disorders should be tested for skin infection and treated according to local management guidelines.

Ocular disorders
Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment with Riltared should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. Riltared should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration. Very rare cases of corneal perforation or ulceration have been reported during use of Riltared.

Interactions with other medicinal products
Potent inducers of CYP3A4 may reduce the efficacy of erlotinib whereas potent inhibitors of CYP3A4 may lead to increased toxicity. Concomitant treatment with these types of agents should be avoided.

Other forms of interactions
Erlotinib is characterised by a decrease in solubility at pH above 5. Medicinal products that alter the pH of the upper Gastro-Intestinal (GI) tract, like proton pump inhibitors, H2 antagonists and antacids, may alter the solubility of erlotinib and hence its bioavailability. Increasing the dose of Riltared when co-administered with such agents is not likely to compensate for the loss of exposure. Combination of erlotinib with proton pump inhibitors should be avoided. The effects of concomitant administration of erlotinib with H2 antagonists and antacids are unknown; however, reduced bioavailability is likely. Therefore, concomitant administration of these combinations should be avoided. If the use of antacids is considered necessary during treatment with Riltared, they should be taken at least 4 hours before or 2 hours after the daily dose of Riltared.

The tablets contain lactose and should not be administered to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Interaction with other medicinal products and other forms of interaction
Erlotinib and other CYP substrates
Erlotinib is a potent inhibitor of CYP1A1, and a moderate inhibitor of CYP3A4 and CYP2C8, as well as a strong inhibitor of glucuronidation by UGT1A1 in vitro.
The physiological relevance of the strong inhibition of CYP1A1 is unknown due to the very limited expression of CYP1A1 in human tissues.
When erlotinib was co-administered with ciprofloxacin, a moderate CYP1A2 inhibitor, the erlotinib exposure [AUC] increased significantly, while no statistically significant change in Cmax was found. Similarly, the exposure to the active metabolite increased for AUC and Cmax. The clinical relevance of this increase has not been established. Caution should be exercised when ciprofloxacin or potent CYP1A2 inhibitors (e.g. fluvoxamine) are combined with erlotinib. If adverse reactions related to erlotinib are observed, the dose of erlotinib may be reduced.
Pre-treatment or co-administration of Riltared did not alter the clearance of the prototypical CYP3A4 substrates, midazolam and erythromycin, but did appear to decrease the oral bioavailability of midazolam. Erlotinib was shown not to affect pharmacokinetics of the concomitantly administered CYP3A4/2C8 substrate paclitaxel. Significant interactions with the clearance of other CYP3A4 substrates are therefore unlikely.
The inhibition of glucuronidation may cause interactions with medicinal products which are substrates of UGT1A1 and exclusively cleared by this pathway. Patients with low expression levels of UGT1A1 or genetic glucuronidation disorders (e.g. Gilbert's disease) may exhibit increased serum concentrations of bilirubin and must be treated with caution.

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 CYP1B1 in tumour tissue also potentially contribute to the metabolic clearance of erlotinib. Potential interactions may occur with active substances which are metabolised by, or are inhibitors or inducers of, these enzymes.
Potent inhibitors of CYP3A4 activity decrease erlotinib metabolism and increase erlotinib plasma concentrations. The concomitant use of erlotinib with ketoconazole (200 mg orally twice daily for 5 days), a potent CYP3A4 inhibitor, resulted in an increase of erlotinib exposure (AUC and Cmax). Therefore, caution should be used when erlotinib is combined with a potent CYP3A4 inhibitor, e.g. azole antifungals (i.e. ketoconazole, itraconazole, voriconazole), protease inhibitors, erythromycin or clarithromycin. If necessary the dose of erlotinib should be reduced, particularly if toxicity is observed.
Potent inducers of CYP3A4 activity increase erlotinib metabolism and significantly decrease erlotinib plasma concentrations. The concomitant use of erlotinib and rifampicin (600 mg orally once daily for 7 days), a potent CYP3A4 inducer, resulted in a decrease in the median erlotinib AUC. Co-administration of Riltared with CYP3A4 inducers should therefore be avoided. For patients who require concomitant treatment with Riltared and a potent CYP3A4 inducer such as rifampicin an increase in dose to 300 mg should be considered while their safety (including renal and liver functions and serum electrolytes) is closely monitored, and if well tolerated for more than 2 weeks, further increase to 450 mg could be considered with close safety monitoring. Reduced exposure may also occur with other inducers e.g. phenytoin, carbamazepine, barbiturates or St. John's Wort (hypericum perforatum). Caution should be observed when these active substances are combined with erlotinib. Alternate treatments lacking potent CYP3A4 inducing activity should be considered when possible.

Erlotinib and coumarin-derived anticoagulants
Interaction with coumarin-derived anticoagulants including warfarin leading to increased International Normalized Ratio (INR) and bleeding events, which in some cases were fatal, have been reported in patients receiving Riltared. Patients taking coumarin-derived anticoagulants should be monitored regularly for any changes in prothrombin time or INR.

Erlotinib and statins
The combination of Riltared and a statin may increase the potential for statin-induced myopathy, including rhabdomyolysis, which was observed rarely.
Erlotinib and smokers
There was a significant reduced AUCinf, Cmax and plasma concentration at 24 hours, respectively, after use of Erlotinib in smokers. Therefore, patients who are still smoking should be encouraged to stop smoking as early as possible before initiation of treatment with Riltared, as plasma erlotinib concentrations are reduced otherwise. No evidence was seen for any benefit of a higher erlotinib dose of 300 mg when compared with the recommended dose of 150 mg in active smokers. Safety were comparable between the 300 mg and 150 mg doses; however, there was a numerical increase in the incidence of rash, interstitial lung disease and diarrhoea, in patients receiving the higher dose of erlotinib.

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 medicinal products altering pH
Erlotinib is characterised by a decrease in solubility at pH above 5. Medicinal products that alter the pH of the upper Gastro-Intestinal (GI) tract may alter the solubility of erlotinib and hence its bioavailability. Co-administration of erlotinib with omeprazole, a proton pump inhibitor (PPI), decreased the erlotinib exposure

[AUC] and maximum concentration [Cmax]. There was no change to Tmax or half-life. Concomitant administration of Riltared with 300 mg ranitidine, an H2-receptor antagonist, decreased erlotinib exposure [AUC] and maximum concentrations [Cmax]. Increasing the dose of Riltared when co-administered with such agents is not likely to compensate for this loss of exposure. However, when Riltared was dosed in a staggered manner 2 hours before or 10 hours after ranitidine 150 mg b.i.d., erlotinib exposure [AUC] and maximum concentrations [Cmax] decreased. The effect of antacids on the absorption of erlotinib has not been investigated but absorption may be impaired, leading to lower plasma levels. In summary, the combination of erlotinib with proton pump inhibitors should be avoided. If the use of antacids is considered necessary during treatment with Riltared, they should be taken at least 4 hours before or 2 hours after the daily dose of Riltared. If the use of ranitidine is considered, it should be used in a staggered manner; i.e. Riltared must be taken at least 2 hours before or 10 hours after ranitidine dosing.

Erlotinib and Gemcitabine
There were no significant effects of gemcitabine on the pharmacokinetics of erlotinib nor were there significant effects of erlotinib on the pharmacokinetics of gemcitabine.

Erlotinib and Carboplatin/Paclitaxel
Erlotinib increases platinum concentrations. The concomitant use of erlotinib with carboplatin and paclitaxel led to an increase of total platinum AUC0-48. the magnitude of this difference is not considered to be clinically relevant. In clinical practice, there may be other co-factors leading to an increased exposure to carboplatin like renal impairment. There were no significant effects of carboplatin or paclitaxel on the pharmacokinetics of erlotinib.

Erlotinib and Capecitabine
Capecitabine may increase erlotinib concentrations. When erlotinib was given in combination with capecitabine, there was a statistically significant increase in erlotinib AUC and a borderline increase in Cmax when compared with values observed in another study in which erlotinib was given as single agent. There were no significant effects of erlotinib on the pharmacokinetics of capecitabine.

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.

Fertility, pregnancy and lactation
Pregnancy
There are no adequate data for the use of erlotinib in pregnant women. Animal data have shown no evidence of teratogenicity or abnormal parturition. However, an adverse effect on the pregnancy cannot be excluded as data from rats and rabbits have shown increased embryo/foetal lethality. The potential risk for humans is unknown.

Women of childbearing potential
Women of childbearing potential must be advised to avoid pregnancy while on Riltared. 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.

Breast-feeding
It is not known whether erlotinib is excreted in human milk. No studies have been conducted to assess the impact of Riltared on milk production or its presence in breast milk. As the potential for harm to the nursing

infant is unknown, mothers should be advised against breast-feeding while receiving Riltared and for at least 2 weeks after the final dose.

Fertility
Animal data have shown no evidence of impaired fertility. However, an adverse effect on the fertility can not be excluded as animal studies have shown effects on reproductive parameters. The potential risk for humans is unknown.

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed; however erlotinib is not associated with impairment of mental ability.

Undesirable effects
Adverse drug reactions are listed by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common, common, uncommon, rare, very rare.
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Non-small cell lung cancer (Riltared administered as monotherapy)
First-Line Treatment of Patients with EGFR Mutations
The most frequent ADRs seen in patients treated with Riltared were rash and diarrhoea, most were Grade 1/2 in severity and manageable without intervention. Grade 3 rash and diarrhoea occurred patients. No Grade 4 rash or diarrhoea was observed. Both rash and diarrhoea resulted in discontinuation of Riltared in patients. Dose modifications (interruptions or reductions) for rash and diarrhoea were needed in of patients

Maintenance treatment
The most frequent ADRs seen in patients treated with Riltared were rash and diarrhoea. No Grade 4 rash or diarrhoea was observed. Rash and diarrhoea resulted in discontinuation of Riltared in patients, while no patients discontinued for rash or diarrhoea. Dose modifications (interruptions or reductions) for rash and diarrhoea were needed in patients.

Second and Further Line Treatment
Rash and diarrhoea 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 Riltared-treated patients and each resulted in discontinuation in patients. Dose reduction for rash and diarrhoea was needed in patients. The median time to onset of rash was 8 days, and the median time to onset of diarrhoea was 12 days.
In general, rash manifests as a mild or moderate erythematous and papulopustular rash, which may occur or worsen in sun exposed areas. For patients who are exposed to sun, protective clothing, and/or use of sunscreen (e.g. mineral-containing) may be advisable.

Pancreatic cancer (Riltared administered concurrently with gemcitabine)
The most common adverse reactions in pancreatic cancer patients receiving Riltared 100 mg plus gemcitabine were fatigue, rash and diarrhoea. Grade 3/4 rash and diarrhoea were each reported in patients with Erlotinib plus gemcitabine. 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 patients, and resulted in discontinuation in patients receiving Riltared plus gemcitabine.

Table 1: Summary of ADRs per frequency category:

Body System	Very common	Common	Uncommon	Rare	Very rare

Eye disorders		-Keratitis -Conjunctivitis	-Eyelash changes [1]		-Corneal perforations -Corneal ulcerations -Uveitis
Respiratory, thoracic and mediastinal disorders		-Epistaxis	-Interstitial lung disease (ILD)[2]		
Gastro-intestinal disorders	-Diarrhoea[6]	-Gastro-intestinal bleeding[3, 6]	-Gastro-intestinal perforations[6]		
Hepato biliary disorders	-Liver function test abnormalities [4]			-Hepatic failure [5]	
Skin and subcutaneous tissue disorders	-Rash	-Alopecia -Dry skin -Paronychia -Folliculitis -Acne/ Dermatitis acneiform -Skin fissures	-Hirsutism -Eyebrow changes -Brittle and Loose nails -Mild skin reactions such as hyperpigmentation	-Palmar plantar erythrodys-aesthesia syndrome	-Stevens-Johnson syndrome/Toxic epidermal necrolysis[6]
Renal and urinary disorders		-Renal insufficiency	-Nephritis -Proteinuria		

[1] Including in-growing eyelashes, excessive growth and thickening of the eyelashes.
[2] Including fatalities, in patients receiving Erlotinib for treatment of NSCLC or other advanced solid tumours. A higher incidence has been observed in patients in Japan.
[3] Some cases have been associated with concomitant warfarin administration and some with concomitant NSAID administration.
[4] Including increased alanine aminotransferase [ALT], aspartate aminotransferase [AST] and bilirubin. These were very common. Cases were mainly mild to moderate in severity, transient in nature or associated with liver metastases.
[5] Including fatalities. Confounding factors included pre-existing liver disease or concomitant hepatotoxic medications.
[6] Including fatalities.

Overdose

Symptoms

Single oral doses of Riltared up to 1000 mg erlotinib in healthy patients, and up to 1600 mg in cancer patients have been tolerated. Repeated twice daily doses of 200 mg in healthy patients were poorly tolerated after only a few days of dosing. Based on the data, severe adverse reactions such as diarrhoea, rash and possibly increased activity of liver aminotransferases may occur above the recommended dose.

Management

In case of suspected overdose, Riltared should be withheld and symptomatic treatment initiated.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agent protein kinase inhibitor, ATC code: L01EB02

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.

Pharmacokinetic properties
Absorption
After oral administration, erlotinib peak plasma levels are obtained in approximately 4 hours after oral dosing. In normal healthy patients, it was 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. It was shown the tumour concentrations of erlotinib averaged 1185 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 tumour at concentrations averaging 160 ng/g tissue, which corresponded to an overall average of 113% 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. 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. It shows that 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.

Pharmacokinetics in special populations
No clinically significant relationship between predicted apparent clearance and patient age, bodyweight, gender and ethnicity were observed. Patient factors, which correlated with erlotinib pharmacokinetics, were serum total bilirubin, AAG and current smoking. Increased serum concentrations of total bilirubin and AAG concentrations were associated with a reduced erlotinib clearance. The clinical relevance of these

differences is unclear. However, smokers had an increased rate of erlotinib clearance. This was confirmed in non-smoking and currently cigarette smoking healthy patients receiving a single oral dose of 150 mg erlotinib. Current smokers achieved erlotinib steady state trough plasma concentration approximately 2-fold less than the former smokers or patients who had never smoked. This effect was accompanied by an increase in apparent erlotinib plasma clearance. At steady-state, it indicated a dose proportional increase in erlotinib exposure when the Riltared dose was increased from 150 mg to the maximum tolerated dose of 300 mg.
Current smokers should be advised to stop smoking while taking Riltared, as plasma concentrations could be reduced otherwise.
The presence of an opioid appeared to increase exposure.
It was demonstrated that covariants affecting erlotinib clearance in patients from the pancreatic patients 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.

Paediatric population
There have been no specific data in paediatric patients.

Elderly population
There have been no specific data in elderly patients.

Hepatic impairment
Erlotinib is primarily cleared by the liver. Although the Cmax was statistically significant lower in moderately hepatic impaired patients, this difference is not considered clinically relevant. No data are available regarding the influence of severe hepatic dysfunction on the pharmacokinetics of erlotinib. Increased serum concentrations of total bilirubin were associated with a slower rate of erlotinib clearance.

Renal impairment
Erlotinib and its metabolites are not significantly excreted by the kidney, as less than 9% of a single dose is excreted in the urine. No clinically significant relationship was observed between erlotinib clearance and creatinine clearance, but there are no data available for patients with creatinine clearance <15 ml/min.

Shelf Life
24 months

Storage conditions
Store below 30°C. This product should not be used after the expiry date (EXP) shown on the pack

Precautions for Storage
Keep out of reach of children

Special precautions for disposal and other handling
No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Nature and contents of container
Aluminium Foil with Clear PVC Film Blister of 10’s tablets and such 3 blisters are placed in a carton with a pack insert

Manufactured in India by:
Dr. Reddy's Laboratories Ltd,

Formulation Unit -VII,
Plot No, P1 to P9, Phase III,
VSEZ, Duvvada,
Visakhapatanam District -530046,
Andhra Pradesh, India.

Product Registration Holder
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Minimum Font size to be used Times New Roman Size 7