ERLOZ (Erlotinib Tablest 150mg)

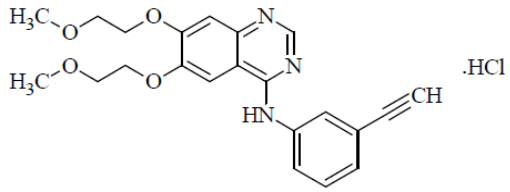
1. Name of the finished pharmaceutical product

ERLOZ (Erlotinib Tablets 150mg)

2. Qualitative and quantitative composition

Each film coated tablet contains, Erlotinib Hydrochloride 163.90 mg, Equivalent to Erlotinib 150 mg.

3. Pharmaceutical form



Dosage form: Film coated Tablet

Description:

Erlotinib Hydrochloride is a White to off-white powder with a molecular weight of 429.90. It is very slightly soluble in water, slightly soluble in methanol and practically insoluble in acetonitrile, acetone, ethyl acetate and Hexane.

4. Clinical particulars

4.1 Therapeutic indications

Non-Small Cell Lung Cancer (NSCLC)

Erlotinib Tablets is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR activating mutations.

4.2 Posology and method of administration

Erlotinib Tablets treatment should be supervised by a physician experienced in the use of anti-cancer therapies.

Patients with Non-Small Cell Lung Cancer

EGFR mutation testing should be performed in accordance with the approved indications.

The recommended daily dose of Erlotinib Tablets is 150 mg taken at least one hour before or two hours after the ingestion of food.

4.3 Special Population

Patients with pancreatic cancer

The recommended daily dose of Erlotinib Tablets is 100 mg taken at least one hour before or two hours after the ingestion of food, in combination with gemcitabine. In patients who do not develop rash within the first 4 – 8 weeks of treatment, further Erlotinib Tablets treatment should be re-assessed

When dose adjustment is necessary, the dose should be reduced in 50 mg steps

Erlotinib Tablets is available in strengths of 25 mg, 100 mg and 150 mg.

Concomitant use of CYP3A4 substrates and modulators may require dose adjustment.

Hepatic impairment

Erlotinib is eliminated by hepatic metabolism and biliary excretion. Although Erlotinib Tablets 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 Erlotinib Tablets to patients with hepatic impairment. Dose reduction or interruption of Erlotinib Tablets should be considered if severe adverse reactions occur. The safety and efficacy of Erlotinib Tablets has not been studied in patients with severe hepatic dysfunction (AST/SGOT and ALT/SGPT> 5 x ULN). Use of Erlotinib Tablets in patients with severe hepatic dysfunction is not recommended.

Renal impairment

The safety and efficacy of Erlotinib Tablets 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 Tablets in patients with severe renal impairment is not recommended.

Paediatric population

The safety and efficacy of erlotinib Tablets in the approved indications has not been established in patients under the age of 18 years. Use of Erlotinib in paediatric patients is not recommended.

Smokers

Cigarette smoking has been shown to reduce Erlotinib Tablets exposure by 50-60%. The maximum tolerated dose of Erlotinib Tablets in NSCLC patients who currently smoke cigarettes was 300 mg. The 300 mg dose did not show improved efficacy in second line treatment after failure of chemotherapy compared to the recommended 150 mg dose in patients who continue to smoke cigarettes. Safety data 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. Current smokers should be advised to stop smoking.

4.4 Contraindications

Hypersensitivity to Erlotinib Tablets or to any of the excipients

4.5 Special warnings and precautions for use

Assessment of EGFR mutation status

When considering the use of Erlotinib Tablets 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 pre specified 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 Tablets 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 Tablets for treatment of non-small cell lung cancer (NSCLC), pancreatic cancer or other advanced solid tumours. In the pivotal study BR.21 in NSCLC, the incidence of ILD (0.8%) was the same in both the placebo and Erlotinib Tablets groups. In a meta-analysis of NSCLC randomised controlled clinical trials (excluding phase I and single-arm phase II studies due to lack of control groups), the incidence of ILD-like events was 0.9% on Erlotinib Tablets compared to 0.4% in patients in the control arms. In the pancreatic cancer study in combination with gemcitabine, the incidence of ILD-like events was 2.5% in the Erlotinib Tablets plus gemcitabine group versus 0.4% in the placebo plus gemcitabine treated group. 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 Tablets 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 (approximately 5% with a mortality rate of 1.5%) is seen among patients in studies conducted in Japan. In patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms such as dyspnoea, cough and fever, Erlotinib Tablets therapy should be interrupted pending diagnostic evaluation. Patients treated concurrently with erlotinib Tablets and gemcitabine should be monitored carefully for the possibility to develop ILD-like toxicity. If ILD is diagnosed, Erlotinib Tablets 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 approximately 50% of patients on Erlotinib Tablets and moderate or severe diarrhoea should be treated with e.g. loperamide. In some cases dose reduction may be necessary. In the clinical studies doses were reduced 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, Erlotinib Tablets 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), Erlotinib Tablets 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.

Hepatotoxicity

Serious cases of drug induced liver injury (DILI) including hepatitis, acute hepatitis and hepatic failure (including fatalities) have been reported during use of Erlotinib Tablets. Risk factors may include pre-existing liver disease or concomitant hepatotoxic medications. Periodic liver function testing is recommended during treatment with Erlotinib Tablets. The frequency of monitoring of liver function should be increased in patients with pre-existing hepatic impairment or biliary obstruction. Prompt clinical evaluation and measurement of liver function tests should be performed in patients who report symptoms that may indicate liver injury. Erlotinib Tablets dosing should be interrupted if changes in liver function are severe . Erlotinib Tablets is not recommended for use in patients with severe hepatic dysfunction.

Gastrointestinal perforation

Patients receiving Erlotinib Tablets 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 Tablets 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. Erlotinib Tablets 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 Erlotinib Tablets should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. Erlotinib Tablets 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 Erlotinib Tablets.

Interactions with other medicinal products

Potent inducers of CYP3A4 may reduce the efficacy of Erlotinib Tablets 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 Tablets 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 Tablets and hence its bioavailability. Increasing the dose of Erlotinib Tablets when co-administered with such agents is not likely to compensate for the loss of exposure. Combination of Erlotinib Tablets with proton pump inhibitors should be avoided. The effects of concomitant administration of Erlotinib Tablets 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 Erlotinib Tablets, they should be taken at least 4 hours before or 2 hours after the daily dose of Erlotinib Tablets.

Excipients with known effect

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (less than 23 mg) per tablet, that is to say Erlotinib Tablets is essentially 'sodium -free'.

4.6 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Erlotinib Tablets and other CYP substrates

Erlotinib Tablets 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 Tablets was co-administered with ciprofloxacin, a moderate CYP1A2 inhibitor, the Erlotinib Tablets exposure [AUC] increased significantly by 39%, while no statistically significant change in Cmax was found. Similarly, the exposure to the active metabolite increased by about 60% and 48% for AUC and Cmax, respectively. 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 Tablets. If adverse reactions related to erlotinib Tablets are observed, the dose of Erlotinib Tablets may be reduced.

Pre-treatment or co-administration of Erlotinib Tablets did not alter the clearance of the prototypical CYP3A4 substrates, midazolam and erythromycin, but did appear to decrease the oral bioavailability of midazolam by up to 24%. In another clinical study, Erlotinib Tablets 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 Tablets 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 Tablets. 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 Tablets metabolism and increase Erlotinib Tablets plasma concentrations. In a clinical study, the concomitant use of erlotinib Tablets with ketoconazole (200 mg orally twice daily for 5 days), a potent CYP3A4 inhibitor, resulted in an increase of Erlotinib Tablets exposure (86% of AUC and 69% of Cmax). Therefore, caution should be used when Erlotinib Tablets 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 Tablets should be reduced, particularly if toxicity is observed.

Potent inducers of CYP3A4 activity increase Erlotinib Tablets metabolism and significantly decrease erlotinib plasma concentrations. In a clinical study, the concomitant use of Erlotinib Tablets and rifampicin (600 mg orally once daily for 7 days), a potent CYP3A4 inducer, resulted in a 69% decrease in the median Erlotinib Tablets AUC. Co-administration of rifampicin with a single 450 mg dose of Erlotinib Tablets resulted in a mean Erlotinib Tablets exposure (AUC) of 57.5% of that after a single 150 mg Erlotinib Tablets dose in the absence of rifampicin treatment. Co-administration of Erlotinib

Tablets with CYP3A4 inducers should therefore be avoided. For patients who require concomitant treatment with Erlotinib Tablets 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 Tablets. Alternate treatments lacking potent CYP3A4 inducing activity should be considered when possible.

Erlotinib Tablets 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 Erlotinib. Patients taking coumarin-derived anticoagulants should be monitored regularly for any changes in prothrombin time or INR.

Erlotinib Tablets and statins

The combination of Erlotinib Tablets and a statin may increase the potential for statin-induced myopathy, including rhabdomyolysis, which was observed rarely.

Erlotinib Tablets and smokers

Results of a pharmacokinetic interaction study indicated a significant 2.8-, 1.5- and 9-fold reduced AUCinf, Cmax and plasma concentration at 24 hours, respectively, after administration of Erlotinib Tablets in smokers as compared to non-smokers. Therefore, patients who are still smoking should be encouraged to stop smoking as early as possible before initiation of treatment with Erlotinib Tablets, as plasma Erlotinib Tablets concentrations are reduced otherwise. Based on the data from the CURRENTS study, no evidence was seen for any benefit of a higher erlotinib Tablets dose of 300 mg when compared with the recommended dose of 150 mg in active smokers. Safety data 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 Tablets.

Erlotinib Tablets and P-glycoprotein inhibitors

Erlotinib Tablets 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. Tablets The consequences of this interaction for e.g. CNS toxicity have not been established. Caution should be exercised in such situations.

Erlotinib Tablets and medicinal products altering pH

Erlotinib Tablets 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 Tablets and hence

its bioavailability. Co-administration of Erlotinib Tablets with omeprazole, a proton pump inhibitor (PPI), decreased the Erlotinib Tablets exposure [AUC] and maximum concentration [Cmax] by 46% and 61%, respectively. There was no change to Tmax or half-life. Concomitant administration of Erlotinib Tablets with 300 mg ranitidine, an H2-receptor antagonist, decreased Erlotinib Tablets exposure [AUC] and maximum concentrations [Cmax] by 33% and 54%, respectively. Increasing the dose of Erlotinib Tablets when co-administered with such agents is not likely to compensate for this loss of exposure. However, when Erlotinib Tablets was dosed in a staggered manner 2 hours before or 10 hours after ranitidine 150 mg b.i.d., Erlotinib Tablets exposure [AUC] and maximum concentrations [Cmax] decreased only by 15% and 17%, respectively. The effect of antacids on the absorption of Erlotinib Tablets has not been investigated but absorption may be impaired, leading to lower plasma levels. In summary, the combination of Erlotinib Tablets with proton pump inhibitors should be avoided. If the use of antacids is considered necessary during treatment with Erlotinib Tablets, they should be taken at least 4 hours before or 2 hours after the daily dose of Erlotinib Tablets. If the use of ranitidine is considered, it should be used in a staggered manner; i.e. Erlotinib Tablets must be taken at least 2 hours before or 10 hours after ranitidine dosing.

Erlotinib Tablets and Gemcitabine

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

Erlotinib Tablets and Carboplatin/Paclitaxel

Erlotinib Tablets increases platinum concentrations. In a clinical study, the concomitant use of Erlotinib Tablets with carboplatin and paclitaxel led to an increase of total platinum AUC0-48 of 10.6%. Although statistically significant, 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 Tablets.

Erlotinib Tablets and Capecitabine

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

Erlotinib Tablets 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 Tablets in pregnant women. Studies in animals have shown no evidence of teratogenicity or abnormal parturition. However, an adverse effect on the pregnancy can not be excluded as rat and rabbit studies 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 Erlotinib Tablets. 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 Tablets is excreted in human milk. No studies have been conducted to assess the impact of Erlotinib Tablets 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 Erlotinib Tablets and for at least 2 weeks after the final dose.

Fertility

Studies in animals 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 Tablets is not associated with impairment of mental ability.

4.7 Undesirable effects

Safety evaluation of Erlotinib Tablets is based on the data from more than 1500 patients treated with at least one 150 mg dose of Erlotinib Tablets monotherapy and more than 300 patients who received Erlotinib Tablets 100 or 150 mg in combination with gemcitabine.

The incidence of adverse drug reactions (ADRs) from clinical trials reported with Erlotinib Tablets alone or in combination with chemotherapy are summarised by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Grade in Table 1. The listed ADRs were those reported in at least 10% (in the Erlotinib Tablets group) of patients and occurred more frequently (≥3%) in patients treated with

Erlotinib Tablets than in the comparator arm. Other ADRs including those from other studies are summarized in Table 2.

Adverse drug reactions from clinical trials (Table 1) and other ADRs (Table 2) are listed by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: 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), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Non-small cell lung cancer (Erlotinib Tablets administered as monotherapy)

First-Line Treatment of Patients with EGFR Mutations

In an open-label, randomised phase III study, ML20650 conducted in 154 patients, the safety of Erlotinib Tablets for first-line treatment of NSCLC patients with EGFR activating mutations was assessed in 75 patients; no new safety signals were observed in these patients.

The most frequent ADRs seen in patients treated with Erlotinib Tablets 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 Tablets in 1% of patients. Dose modifications (interruptions or reductions) for rash and diarrhoea were needed in 11% and 7% of patients, respectively.

Maintenance treatment

In two other double-blind, randomised, placebo-controlled Phase III studies BO18192 (SATURN) and BO25460 (IUNO); Erlotinib Tablets was administered as maintenance after first-line chemotherapy. These studies were conducted in a total of 1532 patients with advanced, recurrent or metastatic NSCLC following first-line standard platinum-based chemotherapy, no new safety signals were identified.

The most frequent ADRs seen in patients treated with Erlotinib Tablets in studies BO18192 and BO25460 were rash (BO18192: all grades 49.2%, grade 3: 6.0%; BO25460: all grades 39.4%, grade 3: 5.0%) and diarrhoea (BO18192: all grades 20.3%, grade 3: 1.8%; BO25460: all grades 24.2%, grade 3: 2.5%). No Grade 4 rash or diarrhoea was observed in either study. Rash and diarrhoea resulted in

discontinuation of Erlotinib Tablets 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.

Second and Further Line Treatment

In a randomised double-blind study (BR.21; Erlotinib Tablets 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 Tablets-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.

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 (Erlotinib Tablets administered concurrently with gemcitabine)

The most common adverse reactions in pivotal study PA.3 in pancreatic cancer patients receiving Erlotinib Tablets 100 mg plus gemcitabine were fatigue, rash and diarrhoea. In the Erlotinib Tablets 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 Tablets plus gemcitabine.

Table 1: ADRs occurring in ≥ 10% of patients in BR.21 (treated with Erlotinib Tablets) and PA.3 (treated with Erlotinib Tablets plus gemcitabine) studies and ADRs occurring more frequently (≥ 3%) than placebo in BR.21 (treated with Erlotinib Tablets) and PA.3 (treated with Erlotinib Tablets plus gemcitabine) studies

		Erlotinib (BR.21) N = 485		**Erlotinib (PA.3) N = 259**			**Frequency category of highest incidence**
NCI-CTC Grade	**Any Grade**	**3**	**4**	**Any Grade**	**3**	**4**	
MedDRA Preferred Term	**%**	**%**	**%**	**%**	**%**	**%**	

Infections and infestations							
Infection*	24	4	0	31	3	<1	very common
Metabolism and nutrition disorders							very common
Anorexia	52	8	1	-	-	-	
Weight decreased	-	-	-	39	2	0	
Eye disorders							very common
Keratoconjunctivitis sicca	12	0	0	-	-	-	very common
Conjunctivitis	12	<1	0	-	-	-	
Psychiatric disorders							very common
Depression	-	-	-	19	2	0	very common
Nervous system disorders							
Neuropathy	-	-	-	13	1	<1	very common
Headache	-	-	-	15	<1	0	
Respiratory, thoracic and mediastinal disorders							
Dyspnoea	41	17	11	-	-	-	very common
Cough	33	4	0	16	0	0	very common
Gastrointestinal disorders							
Diarrhoea**	54	6	<1	48	5	<1	very common
Nausea	33	3	0	-	-	-	very common
Vomiting	23	2	<1	-	-	-	very common
Stomatitis	17	<1	0	22	<1	0	very common
Abdominal pain	11	2	<1	-	-	-	very common
Dyspepsia	-	-	-	17	<1	0	very common
Flatulence	-	-	-	13	0	0	very common
Skin and subcutaneous tissue disorders							very common
Rash***	75	8	<1	69	5	0	very common
Pruritus	13	<1	0	-	-	-	very common
Dry skin	12	0	0	-	-	-	very common
Alopecia	-	-	-	14	0	0	
General disorders and administration site conditions							very common
Fatigue	52	14	4	73	14	2	very common
Pyrexia	-	-	-	36	3	0	very common
Rigors	-	-	-	12	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.

- corresponds to percentage below threshold.

Table 2: Summary of ADRs per frequency category:

Body System	**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)**	**Not known[8]**
Eye disorders		-Keratitis -Conjunctivitis[1]	-Eyelash changes [2]		-Corneal perforations -Corneal ulcerations -Uveitis	
Respiratory, thoracic and mediastinal disorders		-Epistaxis	-Interstitial lung disease (ILD)[3]			
Gastrointestinal disorders	-Diarrhoea[7]	-Gastrointestinal bleeding[4, 7]	-Gastrointestinal perforations[7]	-Pneumatosis intestinalis		
Hepato biliary disorders	-Liver function test abnormalities[5]			-Hepatic failure [6] -Hepatitis		-Acute hepatitis
Skin and subcutaneous tissue disorders	-Rash	-Alopecia -Dry skin[1] -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[7]	
Renal and urinary disorders		-Renal insufficiency[1]	-Nephritis[1] -Proteinuria[1]			

[1] In clinical study PA.3.

[2] Including in-growing eyelashes, excessive growth and thickening of the eyelashes.

[3] Including fatalities, in patients receiving Erlotinib Tablets for treatment of NSCLC or other advanced solid tumours. A higher incidence has been observed in patients in Japan.

[4] In clinical studies, some cases have been associated with concomitant warfarin administration and some with concomitant NSAID administration.

[5] Including increased alanine aminotransferase [ALT], aspartate aminotransferase [AST] and bilirubin. These were very common in clinical study PA.3 and common in clinical study BR.21. Cases were mainly mild to moderate in severity, transient in nature or associated with liver metastases.

[6] Including fatalities. Risk factors may include pre-existing liver disease or concomitant hepatotoxic medications.

[7] Including fatalities.

[8] Cannot be estimated from the available data

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions

4.8 Overdose

Symptoms

Single oral doses of Erlotinib Tablets up to 1000 mg Erlotinib Tablets in healthy subjects, and up to 1600 mg in cancer patients have been tolerated. Repeated twice daily doses of 200 mg in healthy subjects were poorly tolerated after only a few days of dosing. Based on the data from these studies, 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, Erlotinib Tablets should be withheld and symptomatic treatment initiated

5. Pharmacological properties

5.1 Pharmacodynamic properties

Mechanism of action

Erlotinib Tablets is an epidermal growth factor receptor/human epidermal growth factor receptor type 1 (EGFR also known as HER1) tyrosine kinase inhibitor. Erlotinib Tablets 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 Tablets in blocking EGFR-mediated signalling in these EGFR mutation positive tumours is attributed to the tight binding of Erlotinib Tablets 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.

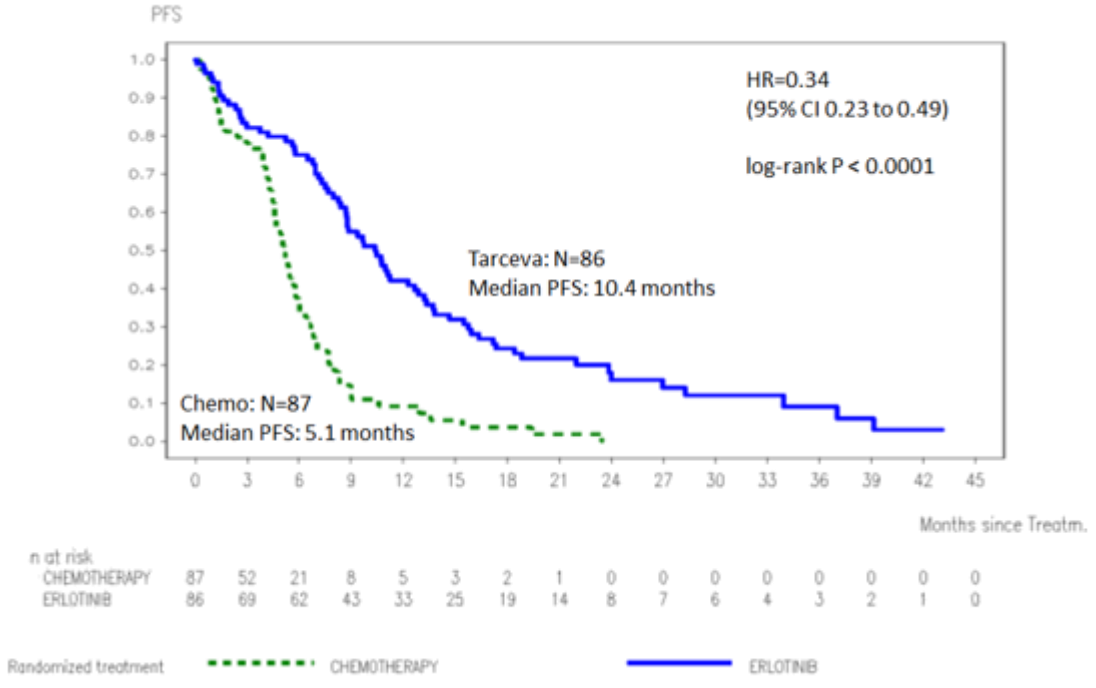
Clinical efficacy

- First-line Non-Small Cell Lung Cancer (NSCLC) therapy for patients with EGFR activating mutations (Erlotinib Tablets administered as monotherapy)

The efficacy of Erlotinib Tablets in first-line treatment of patients with EGFR activating mutations in NSCLC was demonstrated in a phase III, randomised, open-label trial (ML20650, EURTAC). This study was conducted in Caucasian patients with metastatic or locally advanced NSCLC (stage IIIB and IV) who have not received previous chemotherapy or any systemic antitumour therapy for their advanced disease and who present mutations in the tyrosine kinase domain of the EGFR (exon 19 deletion or exon 21 mutation). Patients were randomised 1:1 to receive Erlotinib Tablets 150 mg daily or up to 4 cycles of platinum based doublet chemotherapy.

The primary endpoint was investigator assessed PFS. The efficacy results are summarized in Table 3.

Figure 1: Kaplan-Meier curve for investigator assessed PFS in trial ML20650 (EURTAC) (April 2012 cut-off)



n at risk

CHEMOTHERAPY	87	52	21	8	5	3	2	1	0	0	0	0	0	0	0	0
Erlotinib	86	69	62	43	33	25	19	14	8	7	6	4	3	2	1	0

Randomized treatment ..... CHEMOTHERAPY ERLOTINIB

Table 3: Efficacy results of Erlotinib Tablets versus chemotherapy in trial ML20650 (EURTAC)

		Erlotinib	**Chemo-therapy**	**Hazard Ratio (95% CI)**	**p-value**
Pre-planned Interim Analysis (35% OS maturity) (n=153) Cut-off date: Aug 2010		n=77	n=76		
	Primary endpoint: Progression Free Survival (PFS, median in months)* Investigator Assessed ** Independent Review **	9.4 10.4	5.2 5.4	0.42 [0.27-0.64] 0.47 [0.27-0.78]	p<0.0001 p=0.003
	Best Overall Response Rate (CR/PR)	54.5%	10.5%		p<0.0001
	Overall Survival (OS) (months)	22.9	18.8	0.80 [0.47-1.37]	p=0.4170
Exploratory Analysis (40% OS maturity) (n=173) Cut-off date: Jan 2011		n=86	n=87		
	PFS (median in months), Investigator assessed	9.7	5.2	0.37 [0.27-0.54]	p<0.0001
	Best Overall Response Rate (CR/PR)	58.1%	14.9%		p<0.0001
	OS (months)	19.3	19.5	1.04 [0.65-1.68]	p=0.8702
Updated Analysis (62% OS maturity) (n=173) Cut-off date: April 2012		n=86	n=87		
	PFS (median in months)	10.4	5.1	0.34 [0.23-0.49]	p<0.0001
	OS*** (months)	22.9	20.8	0.93 [0.64-1.36]	p=0.7149

CR=complete response; PR=partial response

* A 58% reduction in the risk of disease progression or death was observed

** Overall concordance rate between investigator and IRC assessment was 70%

*** A high crossover was observed with 82% of the patients in the chemotherapy arm receiving subsequent therapy with an EGFR tyrosine kinase inhibitor and all but 2 of those patients had subsequent Erlotinib Tablets.

Maintenance NSCLC therapy after first-line chemotherapy (Erlotinib Tablets administered as monotherapy)

The efficacy and safety of Erlotinib Tablets as maintenance after first-line chemotherapy for NSCLC was investigated in a randomised, double-blind, placebo-controlled trial (BO18192, SATURN). This study was conducted in 889 patients with locally advanced or metastatic NSCLC who did not progress after 4

cycles of platinum-based doublet chemotherapy. Patients were randomised 1:1 to receive Erlotinib Tablets 150 mg or placebo orally once daily until disease progression. The primary endpoint of the study included progression free survival (PFS) in all patients. Baseline demographic and disease characteristics were well balanced between the two treatment arms. Patients with ECOG PS>1, significant hepatic or renal co-morbidities were not included in the study.

In this study, the overall population showed a benefit for the primary PFS end-point (HR= 0.71 p< 0.0001) and the secondary OS end-point (HR= 0.81 p=0.0088). However the largest benefit was observed in a predefined exploratory analysis in patients with EGFR activating mutations (n= 49) demonstrating a substantial PFS benefit (HR=0.10, 95% CI, 0.04 to 0.25; p<0.0001) and an overall survival HR of 0.83 (95% CI, 0.34 to 2.02). 67% of placebo patients in the EGFR mutation positive subgroup received second or further line treatment with EGFR-TKIs.

The BO25460 (IUNO) study was conducted in 643 patients with advanced NSCLC whose tumors did not harbor an EGFR-activating mutation (exon 19 deletion or exon 21 L858R mutation) and who had not experienced disease progression after four cycles of platinum-based chemotherapy.

The objective of the study was to compare the overall survival of first line maintenance therapy with Erlotinib Tablets versus Erlotinib Tablets administered at the time of disease progression. The study did not meet its primary endpoint. OS of Erlotinib Tablets in first line maintenance was not superior to Erlotinib Tablets as second line treatment in patients whose tumor did not harbor an EGFR-activating mutation (HR= 1.02, 95% CI, 0.85 to 1.22, p=0.82). The secondary endpoint of PFS showed no difference between Erlotinib Tablets and placebo in maintenance treatment (HR=0.94, 95 % CI, 0.80 to 1.11; p=0.48).

Based on the data from the BO25460 (IUNO) study, Erlotinib Tablets use is not recommended for first-line maintenance treatment in patients without an EGFR activating mutation.

<u>NSCLC treatment after failure of at least one prior chemotherapy regimen (Erlotinib</u> Tablets <u>administered as monotherapy</u>)

The efficacy and safety of Erlotinib Tablets as second/third-line therapy was demonstrated in a randomised, double-blind, placebo-controlled trial (BR.21), in 731 patients with locally advanced or metastatic NSCLC after failure of at least one chemotherapy regimen. Patients were randomised 2:1 to receive Erlotinib Tablets 150 mg or placebo orally once daily. Study endpoints included overall survival, progression-free survival (PFS), response rate, duration of response, time to deterioration of lung cancer-related symptoms (cough, dyspnoea and pain), and safety. The primary endpoint was survival.

Demographic characteristics were well balanced between the two treatment groups. About two-thirds of the patients were male and approximately one-third had a baseline ECOG performance status (PS) of 2, and 9% had a baseline ECOG PS of 3. Ninety-three percent and 92% of all patients in the Erlotinib

Tablets and placebo groups, respectively, had received a prior platinum-containing regimen and 36% and 37% of all patients, respectively, had received a prior taxane therapy.

The adjusted hazard ratio (HR) for death in the Erlotinib Tablets group relative to the placebo group was 0.73 (95% CI, 0.60 to 0.87) (p = 0.001). The percent of patients alive at 12 months was 31.2% and 21.5%, for the Erlotinib Tablets and placebo groups, respectively. The median overall survival was 6.7 months in the Erlotinib Tablets group (95% CI, 5.5 to 7.8 months) compared with 4.7 months in the placebo group (95% CI, 4.1 to 6.3 months).

The effect on overall survival was explored across different patient subsets. The effect of Erlotinib Tablets on overall survival was similar in patients with a baseline performance status (ECOG) of 2-3 (HR = 0.77, 95% CI 0.6-1.0) or 0-1 (HR = 0.73, 95% CI 0.6-0.9), male (HR = 0.76, 95% CI 0.6-0.9) or female patients (HR = 0.80, 95% CI 0.6-1.1), patients < 65 years of age (HR = 0.75, 95% CI 0.6-0.9) or older patients (HR = 0.79, 95% CI 0.6-1.0), patients with one prior regimen (HR = 0.76, 95% CI 0.6-1.0) or more than one prior regimen (HR = 0.75, 95% CI 0.6-1.0), Caucasian (HR = 0.79, 95% CI 0.6-1.0) or Asian patients (HR = 0.61, 95% CI 0.4-1.0), patients with adenocarcinoma (HR = 0.71, 95% CI 0.6-0.9) or squamous cell carcinoma (HR = 0.67, 95% CI 0.5-0.9), but not in patients with other histologies (HR 1.04, 95% CI 0.7-1.5), patients with stage IV disease at diagnosis (HR = 0.92, 95% CI 0.7-1.2) or < stage IV disease at diagnosis (HR = 0.65, 95% CI 0.5-0.8). Patients who never smoked had a much greater benefit from Erlotinib Tablets (survival HR = 0.42, 95% CI 0.28-0.64) compared with current or ex-smokers (HR = 0.87, 95% CI 0.71-1.05).

In the 45% of patients with known EGFR-expression status, the hazard ratio was 0.68 (95% CI 0.49-0.94) for patients with EGFR-positive tumours and 0.93 (95% CI 0.63-1.36) for patients with EGFR-negative tumours (defined by IHC using EGFR pharmDx kit and defining EGFR-negative as less than 10% tumour cells staining). In the remaining 55% of patients with unknown EGFR-expression status, the hazard ratio was 0.77 (95% CI 0.61-0.98).

The median PFS was 9.7 weeks in the Erlotinib Tablets group (95% CI, 8.4 to 12.4 weeks) compared with 8.0 weeks in the placebo group (95% CI, 7.9 to 8.1 weeks).

The objective response rate by RECIST in the Erlotinib Tablets group was 8.9% (95% CI, 6.4 to 12.0). The first 330 patients were centrally assessed (response rate 6.2%); 401 patients were investigator-assessed (response rate 11.2%).

The median duration of response was 34.3 weeks, ranging from 9.7 to 57.6+ weeks. The proportion of patients who experienced complete response, partial response or stable disease was 44.0% and 27.5%, respectively, for the Erlotinib Tablets and placebo groups (p = 0.004).

A survival benefit of Erlotinib Tablets was also observed in patients who did not achieve an objective tumour response (by RECIST). This was evidenced by a hazard ratio for death of 0.82 (95% CI, 0.68 to

0.99) among patients whose best response was stable disease or progressive disease.

Erlotinib Tablets resulted in symptom benefits by significantly prolonging time to deterioration in cough, dyspnoea and pain, versus placebo.

In a double-blind, randomised phase III study (MO22162, CURRENTS) comparing two doses of Erlotinib Tablets (300 mg versus 150 mg) in current smokers (mean of 38 pack years) with locally advanced or metastatic NSCLC in the second-line setting after failure on chemotherapy, the 300 mg dose of Erlotinib Tablets demonstrated no PFS benefit over the recommended dose (7.00 vs 6.86 weeks, respectively).

Secondary efficacy endpoints were all consistent with the primary endpoint and no difference was detected for OS between patients treated with Erlotinib Tablets 300 mg and 150 mg daily (HR 1.03, 95% CI 0.80 to 1.32). Safety data 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 Tablets. Based on the data from the CURRENTS study, no evidence was seen for any benefit of a higher Erlotinib Tablets dose of 300 mg when compared with the recommended dose of 25,100 &150 mg in active smokers.

Patients in this study were not selected based on EGFR mutation status.

<u>Pancreatic cancer (Erlotinib Tablets administered concurrently with gemcitabine in study PA.3)</u>

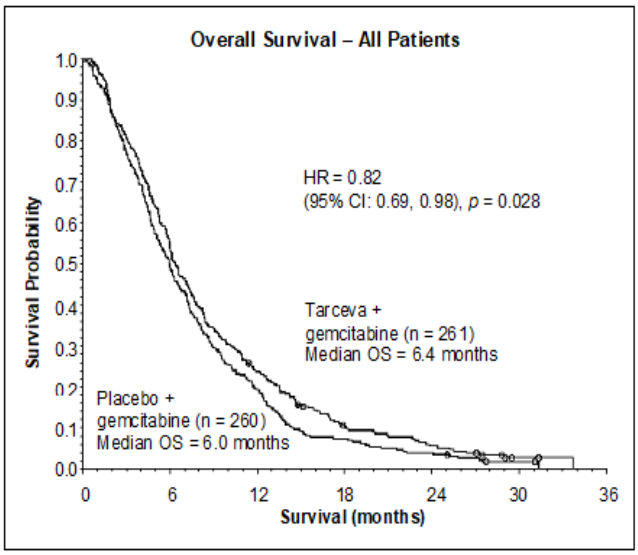
The efficacy and safety of Erlotinib Tablets in combination with gemcitabine as a first-line treatment was assessed in a randomised, double-blind, placebo-controlled trial in patients with locally advanced, unresectable or metastatic pancreatic cancer. Patients were randomised to receive Erlotinib Tablets or placebo once daily on a continuous schedule plus gemcitabine IV (1000 mg/m2, Cycle 1 - Days 1, 8, 15, 22, 29, 36 and 43 of an 8 week cycle; Cycle 2 and subsequent cycles - Days 1, 8 and 15 of a 4 week cycle [approved dose and schedule for pancreatic cancer. Erlotinib or placebo was taken orally once daily until disease progression or unacceptable toxicity. The primary endpoint was overall survival.

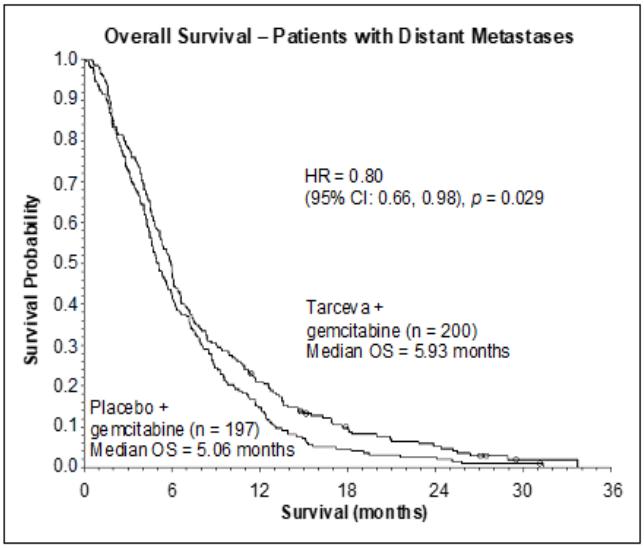
Baseline demographic and disease characteristics of the patients were similar between the 2 treatment groups, 100mg Erlotinib Tablets plus gemcitabine or placebo plus gemcitabine, except for a slightly larger proportion of females in the Erlotinib/gemcitabine arm compared with the placebo/gemcitabine arm:

Baseline	**Erlotinib**	**Placebo**
Females	51%	44%
Baseline ECOG performance status (PS) = 0	31%	32%
Baseline ECOG performance status (PS) = 1	51%	51%
Baseline ECOG performance status (PS) = 2	17%	17%
Metastatic disease at baseline	77%	76%

Survival was evaluated in the intent-to-treat population based on follow-up survival data. Results are shown in the table below (results for the group of metastatic and locally advanced patients are derived from exploratory subgroup analysis).

Outcome	**Erlotinib (months)**	**Placebo (months)**	**Δ (months)**	**CI of Δ**	**HR**	**CI of HR**	***P*- value**
Overall Population							
Median overall survival	6.4	6.0	0.41	-0.54-1.64	0.82	0.69-0.98	0.028
Mean overall survival	8.8	7.6	1.16	-0.05-2.34			
Metastatic Population							
Median overall survival	5.9	5.1	0.87	-0.26-1.56	0.80	0.66-0.98	0.029
Mean overall survival	8.1	6.7	1.43	0.17-2.66			
Locally Advanced Population							
Median overall survival	8.5	8.2	0.36	-2.43-2.96	0.93	0.65-1.35	0.713
Mean overall survival	10.7	10.5	0.19	-2.43-2.69			





In a post-hoc analysis, patients with favourable clinical status at baseline (low pain intensity, good QoL and good PS) may derive more benefit from Erlotinib Tablets. The benefit is mostly driven by the presence of a low pain intensity score.

In a post-hoc analysis, patients on Erlotinib Tablets who developed a rash had a longer overall survival compared to patients who did not develop rash (median OS 7.2 months vs 5 months, HR:0.61).

90% of patients on Erlotinib Tablets developed rash within the first 44 days. The median time to onset of rash was 10 days.

5.2 Pharmacokinetics

Absorption

After oral administration, Erlotinib Tablets 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 Tablets 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 Tablets, tumour samples from surgical excisions on Day 9 of treatment revealed tumour concentrations of Erlotinib Tablets 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 Tablets binds to serum albumin and alpha-1 acid glycoprotein (AAG).

Biotransformation

Erlotinib Tablets 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 Tablets.

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 Tablets produced by O-demethylation of either side chain have comparable potency toErlotinib Tablets in non-clinical in vitro assays and in vivo tumour models. They are present in plasma at levels that are <10% of erlotinib Tablets and display similar pharmacokinetics as Erlotinib Tablets.

Elimination

Erlotinib Tablets 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 Tablets 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.

Pharmacokinetics in special populations

Based on population pharmacokinetic analysis, no clinically significant relationship between predicted apparent clearance and patient age, bodyweight, gender and ethnicity were observed. Patient factors, which correlated with Erlotinib Tablets pharmacokinetics, were serum total bilirubin, AAG and current smoking. Increased serum concentrations of total bilirubin and AAG concentrations were associated with a reduced Erlotinib Tablets clearance. The clinical relevance of these differences is unclear. However, smokers had an increased rate of Erlotinib Tablets clearance. This was confirmed in a pharmacokinetic study in non-smoking and currently cigarette smoking healthy subjects receiving a single oral dose of 150 mg Erlotinib Tablets. The geometric mean of the C_{max} was 1056 ng/mL in the non-smokers and 689 ng/mL in the smokers with a mean ratio for smokers to non-smokers of 65.2% (95% CI: 44.3 to 95.9, p = 0.031). The geometric mean of the AUC0-inf was 18726 ng•h/mL in the non-smokers and 6718 ng•h/mL in the smokers with a mean ratio of 35.9% (95% CI: 23.7 to 54.3, p < 0.0001). The geometric mean of the C24h was 288 ng/mL in the non-smokers and 34.8 ng/mL in the smokers with a mean ratio of 12.1% (95% CI: 4.82 to 30.2, p = 0.0001). In the pivotal Phase III NSCLC trial, current smokers achieved Erlotinib Tablets steady state trough plasma concentration of 0.65 µg/mL (n=16) which was approximately 2-fold less than the former smokers or patients who had never smoked (1.28 µg/mL, n=108). This effect was accompanied by a 24% increase in apparent Erlotinib Tablets plasma clearance. In a phase I dose escalation study in NSCLC patients who were current smokers, pharmacokinetic

analyses at steady-state indicated a dose proportional increase in Erlotinib Tablets exposure when the Erlotinib Tablets dose was increased from 150 mg to the maximum tolerated dose of 300 mg. Steady-state trough plasma concentrations at a 300 mg dose in current smokers in this study was 1.22 µg/mL (n=17).

Based on the results of pharmacokinetic studies, current smokers should be advised to stop smoking while taking Erlotinib Tablets, as plasma concentrations could be reduced otherwise.

Based on population pharmacokinetic analysis, the presence of an opioid appeared to increase exposure by about 11%.

A second population pharmacokinetic analysis was conducted that incorporated Erlotinib Tablets data from 204 pancreatic cancer patients who received Erlotinib Tablets plus gemcitabine. This analysis demonstrated that covariants affecting Erlotinib Tablets 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 Tablets plasma clearance.

Paediatric population

There have been no specific studies in paediatric patients.

Elderly population

There have been no specific studies in elderly patients.

Hepatic impairment

Erlotinib Tablets is primarily cleared by the liver. In patients with solid tumours and with moderately impaired hepatic function (Child-Pugh score 7-9), geometric mean Erlotinib Tablets AUC0-t and C_{max} was 27000 ng•h/mL and 805 ng/mL, respectively, as compared to 29300 ng•h/mL and 1090 ng/mL in patients with adequate hepatic function including patients with primary liver cancer or hepatic metastases. Although the C_{max} 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 Tablets. In population pharmacokinetic analysis, increased serum concentrations of total bilirubin were associated with a slower rate of Erlotinib Tablets clearance.

Renal impairment

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

Preclinical safety data

Chronic dosing effects observed in at least one animal species or study included effects on the cornea (atrophy, ulceration), skin (follicular degeneration and inflammation, redness, and alopecia), ovary (atrophy), liver (liver necrosis), kidney (renal papillary necrosis and tubular dilatation), and gastrointestinal tract (delayed gastric emptying and diarrhoea). Red blood cell parameters were decreased and white blood cells, primarily neutrophils, were increased. There were treatment -related increases in ALT, AST and bilirubin. These findings were observed at exposures well below clinically relevant exposures.

Based on the mode of action, Erlotinib Tablets has the potential to be a teratogen. Data from reproductive toxicology tests in rats and rabbits at doses near the maximum tolerated dose and/or maternally toxic doses showed reproductive (embryo toxicity in rats, embryo resorption and foetotoxicity in rabbits) and developmental (decrease in pup growth and survival in rats) toxicity, but was not teratogenic and did not impair fertility. These findings were observed at clinically relevant exposures.

Erlotinib Tablets tested negative in conventional genotoxicity studies. Two -year carcinogenicity studies with Erlotinib Tablets conducted in rats and mice were negative up to exposures exceeding human therapeutic exposure (up to 2-fold and 10-fold higher, respectively, based on Cmax and/or AUC).

A mild phototoxic skin reaction was observed in rats after UV irradiation.

6 . Pharmaceutical particulars

6.1 List of excipients

Tablets core:

Erlotinib Tablets Hydrochloride, Lactose Monohydrate (Supertab11 SD), Cellulose Microcrystalline (Avicel PH 112), Sodium Starch Glycolate (Primojel), Sodium Lauryl Sulphate(Stepanol WA 100), Magnesium stearate(LIGAMED MF-2-V), Film coating- Opadry White 20B580000: HPMC 2910/Hypromellose, Hydroxypropyl Cellulose, Titanium Dioxide and Macrogol/PEG.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

30’s HDPE Container

7. Marketing authorization holder

Marketed by: HETERO LABS LIMITED, INDIA.

Manufactured by:

HETERO LABS LIMITED

Unit-V, TSIIC Formulation SEZ, Survey No. 411, 425, 435 & 458,

Polepally village, Jadcherla Mandal, Mahaboob Nagar (Dist) – 509301,

Telangana. India.

Category of Distribution: Prescription only medicine- POM