LOTYRO 25/ 100/ 150
CXXXXXX-XX

LOTYRO 25/ 100/ 150
CXXXXXX-XX

LOTYRO 25/ 100/ 150
Erlotinib Film Coated Tablets 25 mg/ 100 mg/ 150 mg

Name of the medicinal product

LOTYRO 25/ 100/ 150

Erlotinib Film Coated Tablets 25 mg/ 100 mg/ 150 mg

Qualitative and quantitative composition

Erlotinib Film Coated Tablets 25 mg/100 mg/ 150 mg
Each film coated tablet contains:
Erlotinib hydrochloride
Equivalent to Erlotinib 25 mg/ 100 mg/ 150 mg
Product contains Lactose
For the full list of excipients, see list of excipients

1. Pharmaceutical form

Film-coated tablet.
Erlotinib Tablets 25 mg
White colored, round shaped, biconvex, film coated tablets, debossed with "E 25" on one side and plain on other side and free from physical defects.
Erlotinib Tablets 100 mg
White colored, round shaped, biconvex, film coated tablets, debossed with "E 100" on one side and plain on other side and free from physical defects.
Erlotinib Tablets 150 mg
White colored, round shaped, biconvex, film coated tablets, debossed with "E 150" on one side and plain on other side and free from physical defects.

2. Clinical particulars

2.1. Therapeutic indications

Non-small cell lung cancer:

Erlotinib is indicated for

- the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer with EGFR activating mutations.
- switch maintenance treatment in patients with locally advanced or metastatic NSCLC with EGFR activating mutations and stable disease after first-line chemotherapy.
- the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with Epidermal Growth Factor Receptor (EGFR)- negative tumours.

Pancreatic cancer:

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

2.2 Dosage and Method of Administration

General

Non-small cell lung cancer:

EGFR mutation testing should be performed prior to initiation of Erlotinib as first-line or maintenance therapy in patients with locally advanced or metastatic NSCLC.
The recommended daily dose of Erlotinib is 150 mg taken at least one hour before or two hours after the ingestion of food.

Pancreatic cancer:

The recommended daily dose of Erlotinib is 100 mg taken at least one hour before or two hours after the ingestion of food, in combination with gemcitabine (see the label 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 2.5).

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 Erlotinib to patients with hepatic impairment. Dose reduction or interruption of Erlotinib should be considered if severe adverse reactions occur. Safety and efficacy have not been studied in patients with severe hepatic impairment (see sections 2.4 Warnings & Precautions [Hepatitis, hepatic failure] and 3.2.5 Pharmacokinetics in Special Populations).

Smokers: Cigarette smoking has been shown to reduce erlotinib exposure by 50-60%. The maximum tolerated dose of Erlotinib in NSCLC patients who currently smoke cigarettes was 300 mg. 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 (see section 2.5, Interactions with other Medicinal Products and other Forms of Interaction and section 3.2.5 Pharmacokinetics in Special Populations).

Renal impairment: The safety and efficacy of Erlotinib has not been studied in patients with renal impairment (see section 3.2.5). Based on pharmacokinetic data, no dose adjustments appear necessary in patients with mild or moderate renal impairment. Use of Erlotinib in patients with severe renal impairment is not recommended.

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

When dose adjustment is necessary, it is recommended to reduce in 50 mg steps (see section 2.4)

2.3 Contraindications

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

2.4 Special Warnings and Special Precautions for Use:

Assessment of EGFR mutation status: When assessing the EGFR mutation status of a patient, it is important that a well-validated and robust methodology is chosen to avoid false negative or false positive determinations.

Interstitial Lung Disease: Cases of interstitial lung disease (ILD) -like events, including fatalities, have been reported uncommonly in patients receiving Erlotinib for treatment of NSCLC (non-small cell lung carcinoma), pancreatic cancer or other advanced solid tumors. In pivotal study BR 21 in NSCLC, the incidence of serious ILD-like events was 0.8% in each of the placebo and Erlotinib arms. In a meta-analysis of NSCLC randomized controlled clinical trials, the incidence of ILD-like events was 0.9% on Erlotinib 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 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 and lung infiltration. These ILD-like events started from a few days to several months after initiating Erlotinib therapy. Most of the cases were associated with confounding or contributing factors such as concomitant or prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections.

In patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever, Erlotinib therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, Erlotinib should be discontinued and appropriate treatment initiated as necessary (see section 2.8).

Diarrhea: Diarrhea has occurred in approximately 50% of patients on Erlotinib and moderate or severe diarrhea should be treated with loperamide. In some cases, dose reduction may be necessary. In the event of severe or persistent diarrhea, nausea, anorexia, or vomiting associated with dehydration, Erlotinib therapy should be interrupted and appropriate measures should be taken to treat the dehydration. (See section 2.8).

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 (concomitant medications, symptoms or diseases or other predisposing conditions including advanced age), Erlotinib therapy should be interrupted and appropriate measures should be taken to intensively rehydrate the patients intravenously. In addition, renal function and serum electrolytes including potassium should be monitored in patients at risk of dehydration.

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. Erlotinib dosing should be interrupted if changes in liver function are severe (see section 2.8, Undesirable Effects).

Gastrointestinal Perforation: Patients receiving Erlotinib are at increased risk of developing gastrointestinal perforation, which was observed uncommonly (including some cases with a fatal outcome). Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at increased risk. Erlotinib should be permanently discontinued in patients who develop gastrointestinal perforation (see section 2.8, Undesirable Effects).

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 (see section 2.8 Undesirable Effects). Erlotinib treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions.

Ocular Disorders: Very rare cases of corneal perforation or ulceration have been reported during use of Erlotinib. Other ocular disorders including abnormal eyelash growth, kerato conjunctivitis sicca or keratitis have been observed with Erlotinib treatment which are also risk factors for corneal perforation/ulceration.

Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/ red eye should be referred promptly to an ophthalmology specialist.

If a diagnosis of ulcerative keratitis is confirmed, treatment with Erlotinib should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. Erlotinib 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.

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

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

Microangiopathic Hemolytic Anemia with Thrombocytopenia: In the pancreatic carcinoma trial, two patients in the Erlotinib /gemcitabine group developed microangiopathic hemolytic anemia with thrombocytopenia (incidence: 0.8%). Both patients received Erlotinib and gemcitabine concurrently. In comparison, in the placebo/gemcitabine group there were no cases of microangiopathic hemolytic anemia with thrombocytopenia.

Drug Interactions: Erlotinib has a potential for clinically significant drug-drug interactions. (See section 2.5, Interactions with other Medicinal Products and other Forms of Interaction)

2.5 Interactions with other Medical Products and other Forms of Interaction

Interaction studies have only been performed in adults.

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.

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. In a clinical study, 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 (86% in median erlotinib exposure [AUC]) and 69 % increase in Cmax when compared to erlotinib alone. 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 or combined CYP3A4/CYP1A2 inhibitors.When Erlotinib was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2, the erlotinib exposure [AUC] and maximum concentration (Cmax) increased by 39% and 17%, respectively. Caution should be exercised when ciprofloxacin or potent CYP1A2 inhibitors (e.g. fluvoxamine) are combined with erlotinib. In these situations, the dose of Erlotinib should be reduced if toxicity is observed.

Potent inducers of CYP3A4 activity increase erlotinib metabolism and significantly decrease erlotinib plasma concentrations. Induction of CYP3A4 metabolism by rifampicin (600 mg p.o. QD for 7 days) resulted in a 69% decrease in the median erlotinib AUC, following a 150 mg dose of Erlotinib, as compared to Erlotinib alone.

Pre-treatment and co-administration of rifampicin with a single 450 mg dose of Erlotinib resulted in a mean erlotinib exposure [AUC] of 57.5% of that after a single 150 mg

Erlotinib dose in the absence of rifampicin treatment. Alternative treatments lacking potent CYP3A4 inducing activity should be considered when possible. For patients who require concomitant treatment with Erlotinib and a potent CYP3A4 inducer such as rifampicin an increase in dose to 300 mg should be considered while their safety (see section 2.4 Special Warnings and Special Precautions) (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. Higher doses have not been studied in this setting. Reduced exposure may also occur with other inducers e.g. phenytoin, carbamazepine, barbiturates or St. Johns Wort (hypericum perforatum). Caution should be observed when these active substances are combined with erlotinib.

Pre-treatment or co-administration of Erlotinib did not alter the clearance of the prototypical CYP3A4 substrates midazolam and erythromycin. Significant interactions with the clearance of other CYP3A4 substrates are therefore unlikely. Oral availability of midazolam did appear to decrease by up to 24%, which was however not attributed to effects on CYP3A4 activity. In another clinical study, 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.

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.

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

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 in smokers as compared to non-smokers (see section 3.2.5). Therefore, patients who are still smoking should be encouraged to stop smoking as early as possible before initiation of treatment with Erlotinib, as plasma erlotinib concentrations are reduced otherwise. The clinical effect of the decreased exposure has not been formally assessed but it is likely to be clinically significant. 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 has not been established. Caution should be exercised in such situations.

Erlotinib is characterised by a decrease in solubility at pH above 5. Drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and hence its bioavailability. Co-administration of Erlotinib with omeprazole, a proton pump inhibitor, decreased the erlotinib exposure [AUC] and Cmax by 46% and 61%, respectively. There was no change to Tmax or half-life. Concomitant administration of Erlotinib with 300 mg ranitidine, an H2-receptor antagonist, decreased erlotinib exposure [AUC] and Cmax by 33% and 54%, respectively. Therefore, co-administration of drugs reducing gastric acid production with Erlotinib should be avoided where possible. Increasing the dose of Erlotinib when co-administered with such agents is not likely to compensate for this loss of exposure. However, when Erlotinib was dosed in a staggered manner 2 hours before or 10 hours after ranitidine 150 mg b.i.d., erlotinib exposure [AUC] and Cmax decreased only by 15% and 17%, respectively. If patients need to be treated with such drugs, then an H2-receptor antagonist such as ranitidine should be considered and used in a staggered manner. Erlotinib must be taken at least 2 hours before or 10 hours after the H2-receptor antagonist dosing.

Smokers should be advised to stop smoking as cigarette smoking, which is known to induce CYP1A1 and CYP1A2, has been shown to reduce erlotinib exposure by 50-60% (See sections 2.2 Special Dosage Instructions, 3.2.5, Pharmacokinetics in Special Populations).
In a Phase Ib study, there were no significant effects of gemcitabine on the pharmacokinetics of erlotinib nor were there significant effects of erlotinib on the pharmacokinetics of gemcitabine.

Erlotinib increases platinum concentrations. In a clinical study, the concomitant use of erlotinib 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.

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.

2.6 Use in Special Populations

2.6.1 Females and Males of Reproductive Potential

Contraception: Females:

Adequate contraceptive methods should be used during therapy, and for at least 2 weeks after completing therapy.

2.6.2 Pregnancy

There are no adequate or well controlled studies in pregnant women using erlotinib. Studies in animals have shown some reproductive toxicity (see sections 3.2.6 Impairment of Fertility and Reproductive toxicity). The potential risk for humans is unknown. Women of childbearing potential must be advised to avoid pregnancy while on erlotinib. Treatment should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the fetus.

2.6.3 Lactation

Nursing mothers: It is not known whether erlotinib is excreted in human milk. No studies have been conducted to assess the impact of erlotinib 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 breastfeeding while receiving erlotinib and for a least 2 weeks after the final dose.

2.6.4 Pediatric Use

The safety and efficacy of erlotinib in the approved indications has not been established in patients under the age of 18 years (see sections 2.2, Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Population)

2.6.5 Geriatric Use

See section 3.2.5, Pharmacokinetics in Special Population.

2.6.6 Renal Impairment

See sections 2.2, Special Dosage Instructions and 3.2.5, Pharmacokinetics in Special Population.

2.6.7 Hepatic Impairment

Erlotinib exposure was similar in patients with moderately impaired hepatic function (ChildPugh score 7-9) compared with patients with adequate hepatic function including patients with primary liver cancer or hepatic metastases (see section 2.4. Special Warnings and Special Precautions). Safety and efficacy have not been studied in patients with severe hepatic impairment. (see section 2.2 Special Dosage Instructions)

2.7 Effects on ability to drive and use machines

Erlotinib has no or negligible influence on the ability to drive and use machines

2.8 Undesirable Effects

2.8.1 Experience from clinical trials

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

The incidence of adverse drug reactions (ADRs) reported with erlotinib alone or in combination with chemotherapy are summarized in the tables below and are based on data from clinical trials. The listed ADRs were those reported in at least 10% (in the erlotinib group) of patients and occurred more frequently (≥3%) in patients treated with erlotinib than in the comparator arm.

Adverse drug reactions from clinical trials (Table 1) 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 <1/1000), very rare (<1/10,000).

- **Non-small cell lung cancer - Erlotinib administered as monotherapy**

First-Line Treatment of Patients with EGFR Mutations

In an open-label, randomized phase III study, ML 20650 conducted in 154 patients, the safety of Erlotinib 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 in study ML 20650 were rash and diarrhoea (any Grade 80% and 57%, respectively), most were Grade 1/2 in severity and manageable without intervention. Grade 3 rash and diarrhoea occurred in 9% and 4% of patients, respectively. No Grade 4 rash or diarrhoea was observed. Both rash and diarrhoea resulted in discontinuation of Erlotinib in 1% of patients. Dose modifications (interruptions or reductions) for rash and diarrhoea were needed in 11% and 7% of patients, respectively.

Maintenance treatment

In two other double-blind, randomized, placebo-controlled Phase III studies (BO18192 (SATURN) and BO25460 (IUNO)) 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 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 in 1% and < 1% of patients, respectively, in study BO18192, while no patient discontinued for rash or diarrhea 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

The ADRs in Table 1 are based on data from a randomized double-blind study (BR.21) conducted in 731 patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Patients were randomized 2:1 to receive Erlotinib 150 mg or placebo. Study drug was taken orally once daily until disease progression or unacceptable toxicity.

The most frequent ADRs were rash and diarrhoea (any Grade 75% and 54%, respectively), most were Grade 1/2 in severity and manageable without intervention. Grade 3/4 rash and diarrhoea occurred in 9% and 6%, respectively, in patients treated with erlotinib and each resulted in study discontinuation in 1% of patients. Dose reduction for rash and diarrhea 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 diarrhea was 12 days.

- **Pancreatic cancer – Erlotinib administered concurrently with gemcitabine**

The ADRs listed in the table 1 below are based on erlotinib-arm data from a controlled clinical trial (PA.3), 259 patients with pancreatic cancer received erlotinib 100 mg plus gemcitabine compared to 256 patients in the placebo plus gemcitabine-arm.

The most frequent ADRs in pivotal study PA.3 in pancreatic cancer patients receiving erlotinib 100 mg plus gemcitabine were fatigue, rash and diarrhea. In the erlotinib plus gemcitabine arm, Grade 3/4 rash and diarrhea were each reported in 5% of patients. The median time to onset of rash and diarrhea was 10 days and 15 days, respectively. Rash and diarrhea each resulted in dose reductions in 2% of patients, and resulted in study discontinuation in up to 1% of patients receiving erlotinib plus gemcitabine.

The Erlotinib 150 mg plus gemcitabine cohort (24 patients) was associated with a higher rate of certain class-specific adverse reactions including rash and required more frequent dose reduction or interruption

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

	Erlotinib Tablets (BR.21) N = 485			Erlotinib Tablets (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							
Anorexia	52	8	1	-	-	-	very common
Weight decreased	-	-	-	39	2	0	very common
Eye disorders							
Keratoconjunctivitis sicca	12	0	0	-	-	-	very common
Conjunctivitis	12	<1	0	-	-	-	very common
Psychiatric disorders							
Depression	-	-	-	19	2	0	very common
Nervous system disorders							
Neuropathy	-	-	-	13	1	<1	very common
Headache	-	-	-	15	<1	0	very common
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							
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	very common
General disorders and administration site conditions							
Fatigue	52	14	4	73	14	2	very common
Pyrexia	-	-	-	36	3	0	very common
Rigors	-	-	-	12	0	0	very common

-corresponds to percentage below threshold

*Severe infections, with or without neutropenia, have included pneumonia, sepsis, and cellulitis

**Can lead to dehydration, hypokalemia and renal failure

***Rash included dermatitis acneiform

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

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

Further information on ADRs of special interest

The following ADRs have been observed in patients who received erlotinib 150 mg as monotherapy or 100 mg or 150 mg in combination with gemcitabine.

Very common ADR's are presented in Table 1, ADR's in other frequency categories are summarized below.

Gastrointestinal Disorders:

Gastrointestinal perforations have been reported uncommonly (in less than 1% of patients) with erlotinib treatment, in some cases with a fatal outcome (see section 2.4 Warnings and Precautions).

Cases of gastrointestinal bleeding have been reported commonly (including some fatalities), some associated with concomitant warfarin administration (See also Section 2.5), and some with concomitant NSAIDs.

Hepatobiliary Disorders:

Liver function test abnormalities (including raised ALT, AST, bilirubin) have been observed commonly in clinical trials of erlotinib. In study PA3, these occurred very commonly. They were mainly mild or moderate in severity, transient in nature or associated with liver metastases.

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.

In study ML20650, at the interim analysis, 7 patients out of a total of 75 patients in the erlotinib arm experienced hepatobiliary disorders, of which five patients had hyperbilirubinaemia, including one event which was considered serious (Grade 2) and assessed as probably related by the investigator. One patient with a pre-existing cholelithiasis experienced a non-serious event of worsening cholelithiasis grade 2, assessed as non-related to study drug and one patient with normal baseline liver function had a fatal event of hepatotoxicity, assessed as related to study drug by the investigator.

Eye Disorders:

Corneal ulcerations or perforations have been reported very rarely in patients receiving erlotinib treatment (see section 2.4 Warnings and Precautions). Keratitis and conjunctivitis has been reported commonly with erlotinib.

Abnormal eyelash growth including; in-growing eyelashes, excessive growth and thickening of the eyelashes have been reported (see section 2.4 Warnings and Precautions).

Respiratory, thoracic and mediastinal disorders:

There have been uncommon reports of serious interstitial lung disease (ILD) -like events, (including fatalities), in patients receiving erlotinib for treatment of NSCLC or other advanced solid tumors. (See section 2.4 Special Warnings and Special Precautions for Use).

Cases of epistaxis have also been reported commonly in both the NSCLC and the pancreatic cancer trials.

Skin and subcutaneous tissue disorders:

Rash has been reported very commonly in patients receiving erlotinib and in general, manifests as a mild or moderate erythematous and papulopustular rash, which may occur or worsen in sun exposed areas. Acne, dermatitis acneiform and folliculitis have been observed commonly, most of these events were mild or moderate and non-serious. For patients who are exposed to sun, protective clothing, and/or use of sun screen (e.g. mineral-containing) may be advisable. Skin fissures, mostly non-serious, were reported commonly and in the majority of cases were associated with rash and dry skin. Other mild skin reactions such as hyperpigmentation have been observed uncommonly (in less than 1% of patients).

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 (see section 2.4 Warnings and Precautions).

Hair and nail changes, mostly non-serious, were reported in clinical trials, e.g. paronychia was reported commonly and hirsutism, eyelash/eyebrow changes and brittle and loose nails were reported uncommonly.

2.8.2 Post-Marketing Experience

The following adverse drug reactions have been identified from postmarketing experience with erlotinib based on spontaneous case reports and literature cases.

Table 2 Adverse drug reactions from postmarketing experience

Adverse reactions	Frequency category
Eye disorders Uveitis	Unknown
Skin and subcutaneous tissue disorders Hair and nail changes, mostly non-serious, e.g. hirsutism, eyelash/eyebrow changes, paronychia and brittle and loose nails	Uncommon

Overdose

Single oral doses of up to 1000 mg 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 events such as diarrhea, rash, and possibly liver transaminase elevation may occur above the recommended dose of 150 mg. In case of suspected overdose Erlotinib should be withheld and symptomatic treatment administered.

3 PHARMACOLOGICAL PROPERTIES

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

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

3.1.2 Efficacy / Clinical studies

Non-Small Cell Lung Cancer (NSCLC): (Erlotinib administered as single agent):

First-line therapy for patients with EGFR activating mutations:

The efficacy of Erlotinib in first-line treatment of patients with EGFR activating mutations in NSCLC was demonstrated in a phase III, randomized, 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 randomized 1:1 to receive erlotinib 150 mg daily or up to 4 cycles of platinum based doublet chemotherapy.

The primary endpoint of investigator assessed PFS was determined at a pre-planned interim analysis (n=153, HR= 0.42, 95 % CI, 0.27 to 0.64; p<0.0001 for the erlotinib group (n=77) relative to the chemotherapy group (n=76)). A 58% reduction in the risk of disease progression or death was observed. In the erlotinib versus chemotherapy arms respectively, median PFS was 9.4 and 5.2 months and Best Overall Response Rate (CR/PR) was 54.5 % and 10.5%, p<0.0001. PFS results were confirmed by an independent review of the scans, median PFS was 10.4 months in the erlotinib group compared with 5.4 months in the chemotherapy group (HR= 0.47, 95% CI, 0.27 to 0.78; p=0.003).

The number of patients included in the investigator assessment of PFS was 129, the number of patients assessed by IRC was 107. The overall concordance rate between investigator and IRC assessment of PFS was 70 %. The overall survival data were immature at the time of interim analysis (HR= 0.80, 95 % CI, 0.47 to 1.37, p=0.4170).

In a further exploratory analysis (n=173) significant benefit was observed in PFS (HR=0.37, 95% CI, 0.27 to 0.54; p<0.0001; median PFS was 9.7 and 5.2 months) and Best Overall Response Rate (58.1 % versus 14.9%, p<0.0001) with erlotinib compared to chemotherapy. Overall survival data were still immature at the time of the exploratory updated analysis (HR= 1.04, 95 % CI, 0.65 to 1.68, p=0.8702).

First-line maintenance therapy:

The efficacy and safety of erlotinib as first-line maintenance therapy of NSCLC was investigated in a randomized, double-blind, placebo-controlled trial BO18192 (SATURN). This study was conducted in 889 patients with locally advanced or metastatic NSCLC who did not progress during 4 cycles of platinum-based doublet chemotherapy. Patients were randomized 1:1 to receive erlotinib 150 mg or placebo orally once daily. The primary end-point of the study was PFS in all patients and in patients with an EGFR IHC positive tumor. Baseline demographic and disease characteristics were well balanced between the two treatment arms.

In this study BO18192 (SATURN), 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 predefine 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. In patients with EGFR wild type tumors (n=388), the PFS HR was 0.78 (95% CI, 0.63 to 0.96; p=0.0185) and the overall survival HR was 0.77 (95% CI, 0.61 to 0.97; p=0.0243).

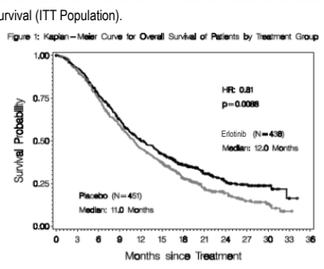
The BO25460 (IUNO) study was conducted in 643 patients with advanced NSCLC whose tumors did not harbor an EGFR-activating mutation (exon 19 deletion or exon 21 L858R mutation) and who had not experienced disease progression after four cycles of platinum-based chemotherapy.

The objective of the study was to compare the overall survival of first line maintenance therapy with erlotinib versus erlotinib administered at the time of disease progression. The study did not meet its primary endpoint. OS of erlotinib in first line maintenance was not superior to erlotinib 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 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 use is not recommended for first-line maintenance treatment in patients without an EGFR activating mutation.

Figure 1 depicts the Kaplan Meier Curves for Overall Survival (ITT Population).

Figure 1: Kaplan–Meier Curve for Overall Survival of Patients by Treatment Group



Note: HR is from a univariate Cox regression model.

The PFS and OS Hazard Ratios, respectively, in patients with EGFR IHC-positive tumors were 0.69 (95% CI: 0.58, 0.82) and 0.77 (95% CI: 0.64, 0.93). The PFS and OS Hazard Ratios in patients with IHC-negative tumors were 0.77 (95% CI: 0.51, 1.14) and 0.91 (95% CI: 0.59, 1.38), respectively.

Patients with adenocarcinoma had an OS Hazard Ratio of 0.77 (95% CI: 0.61, 0.97) and patients with squamous histology had an OS Hazard Ratio of 0.86 (95% CI: 0.68, 1.10).

Second/ Third-line therapy:

The efficacy and safety of erlotinib was demonstrated in a randomised, double -blind, placebo-controlled trial (BR.21 – See figure 1). This study was conducted in 17 countries, 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 150 mg or placebo orally once daily. Study end points included overall survival, time to deterioration of lung cancer-related symptoms (cough, dyspnea and pain), response rate, duration of response, progression-free survival (PFS), and safety. The primary end-point was survival.

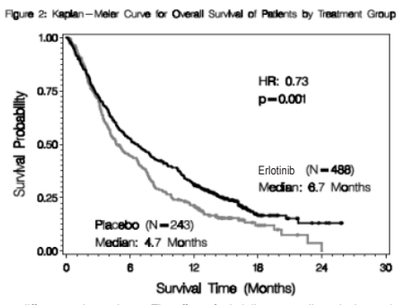
Due to the 2:1 randomisation, 488 patients were randomised to erlotinib and 243 patients to placebo. Patients were not selected for HER1/EGFR status, gender, race, smoking history and histologic classification.

Demographic characteristics were well balanced between the two treatment arms. 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 of 3. Ninety-three percent and 92% of all patients in the erlotinib 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. Fifty percent of the patients had received only one prior regimen of chemotherapy.

Survival was evaluated in the intent-to-treat population. The median overall survival improved by 42.5% and was 6.7 months in the erlotinib group (95% CI, 5.5 – 7.8 months) compared with 4.7 months in the placebo group (95% CI, 4.1 to 6.3 months). The primary survival analysis was adjusted for the stratification factors as reported at the time of randomisation (ECOG PS, best response to prior therapy, number of prior regimens, and exposure to prior platinum) and HER1/EGFR status. In this primary analysis, the adjusted hazard ratio for death in the erlotinib group relative to the placebo group was 0.73 (95% CI, 0.60 to 0.87) (p = 0.001). The percentage of patients alive at 12 months was 31.2% and 21.5%, respectively.

Figure 2

Figure 2: Kaplan–Meier Curve for Overall Survival of Patients by Treatment Group



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

Analysis of the impact of EGFR expression status on the treatment effect on clinical outcome is limited because EGFR status is known for 326 NSCLC study patients (45%). EGFR status was ascertained for patients who already had tissue samples prior to study enrolment. However, the survival in the EGFR tested population and the effects of single - agent erlotinib were almost identical to that in the entire study population, suggesting that the tested population was a representative sample. A positive EGFR expression status was defined as having at least 10% of cells staining for EGFR in contrast to the 1% cut-off specified in the EGFR pharmDx kit instructions. The use of the pharmDx kit has not been validated for use in non-small cell lung cancer.

Single-agent erlotinib prolonged survival in the EGFR positive subgroup (N=185; HR=0.68; 95% CI = 0.49-0.94) and the subgroup whose EGFR status was unmeasured (N=405; HR=0.77; 95% CI = 0.61-0.98), but did not appear to have an effect on survival in the EGFR negative subgroup (N=141; HR=0.93; 95% CI = 0.63=1.36). However, the confidence intervals for the EGFR positive, negative and unmeasured subgroups of NSCLC patients are wide and overlap, so that a survival benefit due to erlotinib in the EGFR negative subgroup cannot be excluded.

For the subgroup of NSCLC patients who never smoked, EGFR status also appeared to be predictive of erlotinib survival benefit. Patients who never smoked and were EGFR positive had a large erlotinib survival benefit (N=41; HR=0.28; 95% CI = 0.13-0.61). There were too few EGFR negative patients who never smoked to reach a conclusion. Tumour responses were observed in all EGFR subgroups: 11.3% in the EGFR positive subgroup, 9.5% in the EGFR unmeasured subgroup and 3.8% in the EGFR negative subgroup. An improvement in progression free survival was demonstrated in the EGFR positive subgroup (HR=0.49; 95% CI = 0.35-0.68), the EGFR unmeasured subgroup (HR=0.60; 95% CI = 0.47-0.75), and less certain in the EGFR negative subgroup (HR=0.80; 95% CI = 0.55-1.16).

A survival benefit of erlotinib was also observed in patients who did not achieve an objective tumor response (by RECIST). This was evidenced by a hazard ratio for death of 0.82 (95% CI, 0.68-0.99) among patients whose best response was stable disease or progressive disease.

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

The median PFS was 9.7 weeks in the erlotinib group (95% CI, 8.4 – 12.4 weeks) compared with 8.0 weeks in the placebo group (95% CI, 7.9 to 8.1 weeks). The HR for progression, adjusted for stratification factors and HER1/EGFR status, was 0.61 (95% CI, 0.51 to 0.73) (p < 0.001). The percent of PFS at 6-months was 24.5% and 9.3%, respectively, for the erlotinib and placebo arms.

The objective response rate by RECIST in the erlotinib group was 8.9% (95% CI, 6.4 to 12.0%). The median duration of response was 34.3 weeks, ranging from 9.7 to 57.6+ weeks. Two responses (0.9%, 95% CI, 0.1 to 3.4) were reported in the placebo group. The proportion of patients who experienced complete response, partial response or stable disease was 44.0% and 27.5%, respectively, for the erlotinib and placebo groups (p=0.004).

In a double-blind, randomized phase III study (MO22162, CURRENTS) comparing two doses of erlotinib (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 demonstrated no PFS benefit over the recommended dose (7.00 vs 6.86 weeks, respectively). Patients in this study were not selected based on EGFR mutation status.

Results from two multicentre, placebo-controlled, randomised trials in over 1000 patients conducted in first-line patients with locally advanced or metastatic NSCLC showed no clinical benefit with the concurrent administration of erlotinib with platinum-based chemotherapy [carboplatin and paclitaxel (erlotinib, N = 526) or gemcitabine and cisplatin (erlotinib, N = 580)]. Its use is not recommended in that setting.

Pancreatic cancer (Erlotinib administered concurrently with gemcitabine).

The efficacy and safety of erlotinib in combination with gemcitabine as a first line treatment was assessed in a randomized, double blind, placebo-controlled trial in 569 patients with locally advanced, unresectable or metastatic pancreatic cancer. Patients were randomized 1:1 to receive erlotinib (100 mg or 150 mg) or placebo once daily on a continuous schedule plus gemcitabine i.v. (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, see the gemcitabine SPC]). erlotinib or placebo was taken orally once daily until disease progression or unacceptable toxicity. Study end points included overall survival, response rate and progression-free survival (PFS). Duration of response was also examined. The primary endpoint was survival. A total of 285 patients were randomized to receive gemcitabine plus erlotinib (261 patients in the 100 mg cohort and 24 patients in the 150 mg cohort) and 284 patients were randomized to receive gemcitabine plus placebo (260 patients in the 100 mg cohort and 24 patients in the 150 mg cohort). Too few observations were made for the 150 mg cohort to draw conclusions.

Baseline demographic and disease characteristics of the patients were similar between the 2 treatment groups, 100 mg erlotinib plus gemcitabine or placebo plus gemcitabine, except for a slightly larger proportion of females in the erlotinib arm (51%) compared with the placebo arm (44%). The median time from initial diagnosis to randomization was approximately 1.0 month. Approximately half of the patients had a baseline ECOG performance status (PS) of 1, and 17 % had a baseline ECOG PS of 2. Most patients presented with metastatic disease at study entry as the initial manifestation of pancreatic cancer (77% in the erlotinib arm, 76% in the placebo arm).

Survival was evaluated in the intent-to-treat population based on follow-up survival data including 551 deaths. Results are presented for the 100 mg dose cohort (504 deaths). The adjusted hazard ratio for death in the erlotinib group relative to the placebo group was 0.82 (95 % CI, 0.69 to 0.98) (p = 0.028). The percent of patients alive at 12 months was 23.8 % in the erlotinib group compared to 19.4% in the placebo group. The median overall survival was 6.4 months in the erlotinib group compared with 6 months in the placebo group (see figure 2).

The table below summarizes the results of the study.

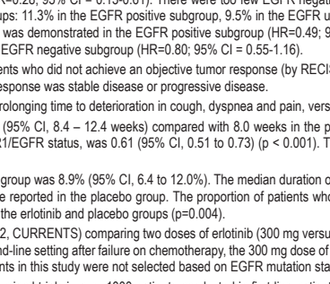
Table 3: Study PA3 Efficacy Results

	Erlotinib 100mg plus gemcitabine (N = 261)	Placebo plus gemcitabine (N=260)	p-value
Median survival	6.4 months	6 months	
Hazard ratio, mortality (erlotinib:placebo) (95% CI)	0.82 (0.69 to 0.98)		p = 0.028
% Patients alive at 12 months	23.8	19.4	

The median PFS was 3.81 months (16.5 weeks) in the erlotinib group (95 % CI, 3.58 to 4.93 months) compared with 3.55 months (15.2 weeks) in the placebo group (95 % CI, 3.29 to 3.75 months) (p = 0.006).

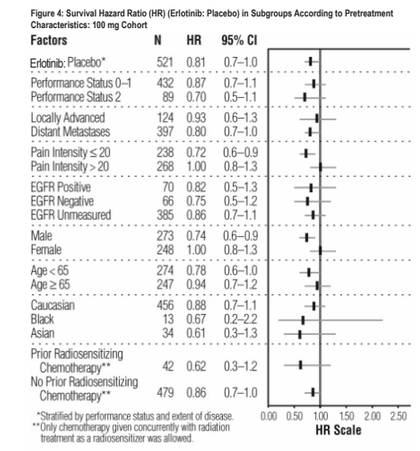
The median duration of response was 23.9 weeks, ranging from 3.71 to 56+ weeks. The objective response rate (complete response and partial response) was 8.6 % in the erlotinib group and 7.9% in the placebo group. The proportion of patients who experienced complete response, partial response or stable disease was 59 % and 49.4 %, respectively, for the erlotinib and placebo groups (p = 0.036)

Figure 3: Kaplan–Meier Curve for Overall Survival: 100 mg Cohort



In a series of exploratory univariate subset analyses (the stratification factors at randomization and at baseline, as well as pain intensity by visual analog score, EGFR status, gender, age, race, and any prior chemotherapy), all of the HRs in the erlotinib plus gemcitabine arm relative to the placebo plus gemcitabine arm were less than or equal to 1.0 suggesting consistency across all patient subsets. However, in patients with pain intensity score >20, female, locally advanced, age ≥65 years, or performance status 0 or 1, the benefit of erlotinib was uncertain.

Figure 4: Survival Hazard Ratio (HR) (Erlotinib: Placebo) in Subgroups According to Pretreatment Characteristics: 100 mg Cohort



Note: Depicted are the univariate hazard ratio (HR) for death in the patients receiving erlotinib plus gemcitabine relative to the patients receiving placebo plus gemcitabine, the 95% confidence interval (CI) for the HR, and the sample size (N) in each subgroup. The hash mark on the horizontal bar represents the HR, and the length of the horizontal bar represents the 95% confidence interval. A hash mark to the left of the vertical line corresponds to a HR that is less than 1.00, which indicates that survival is better in the erlotinib arm compared with the placebo arm in that subgroup. Only chemotherapy given concurrently with radiation treatment as a radiosensitizer was allowed.

3.2 Pharmacokinetic Properties

3.2.1 Absorption

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

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

3.2.2 Distribution

Erlotinib has a mean apparent volume of distribution of 232 l and distributes into tumor 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, tumor samples from surgical excisions on Day 9 of treatment revealed tumor concentrations of erlotinib that averaged 1,185 ng/g of tissue. This corresponded to an overall average of 63% of the steady state observed peak plasma concentrations. The primary active metabolites were present in tumor at concentrations averaging 160 ng/g tissue, which corresponded to an overall average of 113% of the observed steady state peak plasma concentrations. Tissue distribution studies using whole body autoradiography following oral administration with [14C] labeled erlotinib in athymic nude mice with HN5 tumor xenografts have shown rapid and extensive tissue distribution with maximum concentrations of radiolabeled drug (approximately 73% of that in plasma) observed at 1 hour.

3.2.3 Metabolism

Erlotinib is metabolised in humans by hepatic cytochrome P450 enzymes, primarily by CYP3A4 and to a lesser extent by CYP1A2. Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung, and CYP1B1 in tumour tissue potentially contribute to the metabolic clearance of erlotinib. In vitro studies indicate approximately 80-95% of erlotinib metabolism is by the CYP3A4 enzyme. There are three main metabolic pathways identified: 1) O-demethylation of either side chain or both, followed by oxidation to the carboxylic acids; 2) oxidation of the acetylene moiety followed by hydrolysis to the aryl carboxylic acid; and 3) aromatic hydroxylation of the phenyl-acetylene moiety. The primary metabolites of erlotinib produced by O-demethylation of either side chain have comparable potency to erlotinib in nonclinical in vitro assays and in vivo tumor models. They are present in plasma at levels that are <10% of erlotinib and display similar pharmacokinetics as erlotinib. The metabolites and trace amounts of erlotinib are excreted predominantly via the feces (>90%), with renal elimination accounting for only a small amount of an oral dose.

3.2.4 Elimination

Clearance:

A population pharmacokinetic analysis in 591 patients receiving single agent erlotinib show 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. No significant relationships between predicted apparent clearance and patient age, body weight, gender, and ethnicity were observed.

Patient factors, which correlate with erlotinib pharmacokinetics, are serum total bilirubin, AAG concentrations and current smoking. Increased serum concentrations of total bilirubin and AAG concentrations were associated with a slower rate of erlotinib clearance. Smokers had a higher rate of erlotinib clearance.

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

Exposure:

Following a 150 mg oral dose of erlotinib, at steady state, the median time to reach maximum plasma concentrations is approximately 4.0 hours with median maximum plasma concentrations achieved of 1,995 ng/ml. Prior to the next dose at 24 hours, the median minimum plasma concentrations are 1,238 ng/ml. Median AUC achieved during the dosing interval at steady state are 41,300 mcg*hr/ml.

3.2.5 Pharmacokinetics in special populations

There have been no specific studies in pediatric or elderly patients.

Hepatic impairment: Erlotinib is mainly cleared by the liver. Erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh score 7-9) compared with patients with adequate hepatic function including patients with primary liver cancer or hepatic metastases.

Renal impairment: Erlotinib and its metabolites are not significantly excreted by the kidneys, as less than 9% of a single dose is excreted in the urine. No clinical studies have been conducted in patients with compromised renal function.

Smokers: A pharmacokinetic study in nonsmoking and currently cigarette smoking healthy subjects has shown that cigarette smoking leads to increased clearance of, and decreased exposure to, erlotinib.

The geometric mean of the Cmax 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 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 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 exposure when the erlotinib dose was increased from 150 mg to the maximum tolerated dose of 300 mg. Steady-state trough plasma concentrations at a 300mg 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, as plasma concentrations could be reduced otherwise.

3.2.6 Preclinical safety data

Carcinogenicity

Evidence for a carcinogenic potential was not seen in nonclinical studies. Erlotinib was neither genotoxic nor clastogenic in genetic toxicity studies. Two-year carcinogenicity studies with erlotinib conducted in rats and mice at exposures exceeding human therapeutic exposure were negative.

Genotoxicity

Erlotinib was negative in the standard battery of genotoxicity assays.

Impairment of Fertility

Impairment of fertility was not observed in studies with male and female rats at doses near the MTD levels.

Reproductive Toxicity

Data from reproductive toxicology tests in rats and rabbits indicate that, following exposure to erlotinib at doses near the MTD and/or doses that were maternally toxic, there was embryotoxicity, but there was no evidence of teratogenicity, or abnormal pre- or postnatal physical or behavioral development. Maternal toxicity in both rats and rabbits in these studies occurred at plasma exposure levels that were similar to those in humans following a 150 mg dose of erlotinib.

Other

Chronic dosing effects observed in at least 1 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 diarrhea). Red blood cell (RBC) counts, hematocrit and hemoglobin were decreased and reticulocytes were increased. White blood cells (WBCs), primarily neutrophils, were increased. There were treatment-related increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin.

In vitro studies of erlotinib showed inhibition of hERG channels at concentrations at least 20 times higher than the free drug concentration in humans at therapeutic doses. Studies in dogs did not show QT-prolongation. A systematic centralized review of ECG data from 152 individuals from seven studies with healthy volunteers found no evidence of QT prolongation, and clinical studies have found no evidence of arrhythmias, associated with QT prolongation.

Pharmaceutical particulars

List of excipients

Tablet core:

Microcrystalline Cellulose, Sodium Lauryl Sulfate, Sodium starch glycollate Type A, Magnesium Stearate, Lactose Monohydrate(Lactochem fine powder), Lactose Monohydrate(Supertab 11 SD) .

Tablet coating:

Opadry white 20H580004 (HPMC 2910/Hypromellose, Hydroxypropyl cellulose, Titanium dioxide and Propylene glycol)and Purified water.

Incompatabilities

Not applicable.

Special precautions for storage

Store below 30°C.

Keep out of the sight and reach of children.

Nature and contents of container

30 tablets for HDPE container with polypropylene cap

1x10, 3x10 and 10x10 Alu-PVC blister pack

Not all pack sizes may be marketed.

Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Manufactured by:

MSN LABORATORIES PRIVATE LIMITED

Formulations Division, Unit-II, Sy. No. 1277 & 1319 to 1324,

Nandigama (Village & Mandal),

Rangareddy District - 509 228,

Telangana, INDIA.

Product Registrant:

GOLDPLUS UNIVERSAL PTE LTD,

103 Kallang Avenue,

#06-02, Singapore 339504

Date of Revision: August 2024

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