Tarceva®

Erlotinib hydrochloride

1. DESCRIPTION

1.1 THERAPEUTIC/PHARMACOLOGIC CLASS OF DRUG
Anti-neoplastic agent
ATC code L01EB02

1.2 TYPE OF DOSAGE FORM
Film-coated tablets

1.3 ROUTE OF ADMINISTRATION
Oral

1.4 STERILE/RADIOACTIVE STATEMENT
Not applicable

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION
Active ingredient: erlotinib hydrochloride.
Each 100 mg film-coated tablet contains 100 mg erlotinib as erlotinib hydrochloride.
Each 150 mg film-coated tablet contains 150 mg erlotinib as erlotinib hydrochloride.

2. CLINICAL PARTICULARS
2.1 THERAPEUTIC INDICATION(S)

Non-Small Cell lung cancer
Tarceva is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC stage IIIb/IV) with EGFR activating mutations (exon 19 deletions or exon 21 (L858R) mutations).

Tarceva is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.
When prescribing Tarceva, factors associated with prolonged survival should be taken into account.

No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with EGFR-negative tumours.

Pancreatic cancer
Tarceva in combination with gemcitabine is indicated for the treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.
When prescribing Tarceva, factors associated with prolonged survival should be taken into account.

No survival advantage could be shown for patients with locally advanced disease (the median overall survival was 6.4 months in the Tarceva group compared with 6 months in the placebo group).

2.2 DOSAGE AND ADMINISTRATION

General

Tarceva treatment should be supervised by a physician experienced in the use of anticancer therapies.

Non-small cell lung cancer:
EGFR mutation testing should be performed prior to initiation of Tarceva therapy in chemo-naïve patients with advanced or metastatic NSCLC.

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

Pancreatic cancer:
The recommended daily dose of Tarceva is 100 mg taken at least one hour before or two hours after the ingestion of food, in combination with gemcitabine (see the summary of product characteristics of gemcitabine for the pancreatic cancer indication). In patients who do not develop rash within the first 4–8 weeks of treatment, further Tarceva treatment should be re-assessed (see section *3.1 Pharmacodynamic Properties*).

When dose adjustment is necessary, reduce in 50 mg steps (see section *2.4 Warning and Precautions*).

Tarceva is available in strengths of 100 mg and 150 mg.

2.2.1 Special Dosage Instructions

Drug Interactions: Concomitant use of CYP3A4 substrates and modulators may require dose adjustment (see section *2.8 Interaction with Other Medicinal Products and Other Forms of Interaction*).

When dose adjustment is necessary, it is recommended to reduce in 50 mg steps (see sections *2.4 Warnings and Precautions* and *2.8 Interactions with Other Medicinal Products and Other Forms of Interaction*).

Hepatic Impairment: Erlotinib is eliminated by hepatic metabolism and biliary excretion. Although erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh score 7-9) compared with patients with adequate hepatic function, caution should be used when administering Tarceva to patients with hepatic impairment. Dose reduction or interruption of Tarceva should be considered if severe adverse reactions occur. The safety and efficacy of erlotinib has not been studied in patients with severe hepatic dysfunction (AST/SGOT and ALT/SGPT > 5 x ULN). Use of Tarceva in patients with severe hepatic dysfunction is not recommended.

Renal impairment: The safety and efficacy of erlotinib has not been studied in patients with renal impairment (serum creatinine concentration > 1.5 times the upper normal limit). Based on pharmacokinetic data no dose adjustments appear necessary in patients with mild or moderate renal impairment (see section *3.2 Pharmacokinetic Properties*). Use of Tarceva in patients with severe renal impairment is not recommended.

Paediatric use: The safety and efficacy of erlotinib has not been studied in patients under the age of 18 years. Use of Tarceva in paediatric patients is not recommended.

Smokers: Cigarette smoking has been shown to reduce erlotinib exposure by 50-60%. The maximum tolerated dose of Tarceva 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 sections *2.8 Interactions with Other Medicinal Products and Other Forms of Interaction* and *3.2.5 Pharmacokinetics in Special Populations*)

2.3 CONTRAINDICATIONS

Tarceva is contraindicated in patients with severe hypersensitivity to erlotinib or to any of the excipients.

2.4 WARNINGS AND PRECAUTIONS

2.4.1 General

Interstitial Lung Disease: Cases of interstitial lung disease (ILD)-like events, including fatalities, have been reported uncommonly in patients receiving Tarceva 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 serious ILD-like events was 0.8% in each of the placebo and Tarceva arms.

In a meta-analysis of NSCLC randomized controlled clinical trials, the incidence of ILD-like events was 0.9% on Tarceva 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 Tarceva plus gemcitabine group versus 0.4% in the placebo plus gemcitabine treated group.

Some examples of reported diagnoses in patients suspected of having ILD-like events include pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome (ARDS), lung infiltration, and alveolitis. This ILD-like events started from a few days to several months after initiating Tarceva 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 dyspnoea, cough and fever, Tarceva therapy should be interrupted pending diagnostic evaluation. Patients treated concurrently with erlotinib and gemcitabine should be monitored carefully for the possibility to develop ILD-like toxicity. If ILD is diagnosed, Tarceva should be discontinued and appropriate treatment initiated as necessary (see section *2.6 Undesirable Effects*).

Diarrhoea, Dehydration, Electrolyte Imbalance and Renal Failure: Diarrhoea has occurred in approximately 50% of patients on Tarceva, 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, Tarceva therapy should be interrupted and appropriate measures should be taken to treat the dehydration (see

section *2.6 Undesirable Effects*). There have been rare reports of hypokalaemia and renal failure (including fatalities). Some report of renal failure 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), Tarceva therapy should be interrupted and appropriate measures should be taken to intensively rehydrate the patients intravenously. In addition, renal function and serum electrolytes including potassium should be monitored in patients at risk of dehydration.

Hepatitis, hepatic failure: Rare cases of hepatic failure (including fatalities) have been reported during use of Tarceva. Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medications. Therefore, in such patients, periodic liver function testing should be considered. Tarceva dosing should be interrupted if changes in liver function are severe (see section *2.6 Undesirable Effects*).

Gastrointestinal Perforation: Patients receiving Tarceva 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. Tarceva should be permanently discontinued in patients who develop gastrointestinal perforation (see section *2.6 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 *2.6 Undesirable Effects*). Tarceva 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: Very rare cases of corneal perforation or ulceration have been reported during use of Tarceva. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with Tarceva treatment which are also risk factors for corneal perforation/ulceration. Tarceva therapy should be interrupted or discontinued if patients present with acute/worsening ocular disorders such as eye pain (see section *2.6 Undesirable Effects*).

Drug Interactions: Tarceva has a potential for clinically significant drug-drug interactions. (See section *2.8 Interactions with Other Medicinal Products and Other Forms of Interaction*).

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

2.4.2 Drug Abuse and Dependence

Not applicable.

2.4.3 Ability to Drive and Use Machines

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

2.5 USE IN SPECIAL POPULATIONS

2.5.1 Females and Males of Reproductive Potential

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

2.5.2 Pregnancy

There are no adequate or well controlled studies in pregnant women using Tarceva. Studies in animals have shown some reproductive toxicity (see sections *3.3.3 Impairment of Fertility* and *3.3.4 Reproductive Toxicity*). The potential risk for humans is unknown. Women of childbearing potential must be advised to avoid pregnancy while on Tarceva. Treatment should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the fetus.

2.5.3 Lactation

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

2.5.4 Pediatric Use

The safety and efficacy of Tarceva in the approved indications has not been established in patients under the age of 18 years (see sections *2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Population*).

2.5.5 Geriatric Use

See section *3.2.5 Pharmacokinetics in Special Population.*

2.5.6 Renal Impairment

See sections *2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Population.*

2.5.7 Hepatic Impairment

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 (see section *2.4.1 Warnings and Precautions*). Safety and efficacy have not been studied in patients with severe hepatic impairment (see section *2.2.1 Special Dosage Instructions*).

2.6 UNDESIRABLE EFFECTS

2.6.1 Clinical Trials

Safety evaluation of Tarceva is based on the data from more than 1200 patients treated with at least one 150 mg dose of Tarceva monotherapy, and more than 300 patients who received Tarceva 100 mg or 150 mg in combination with gemcitabine.

The incidence of adverse drug reactions (ADRs) reported with Tarceva 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 Tarceva group) of patients and occurred more frequently (> 3%) in patients treated with Tarceva 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 (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000), very rare (< 1/10000).

- **Non-small cell lung cancer-Tarceva 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 Tarceva 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 Tarceva 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 Tarceva in 1% of patients. Dose modifications (interruptions or reductions) for rash and diarrhoea were needed in 11% and 7% of patients, respectively.

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 Tarceva 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 Tarceva 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.

- **Pancreatic cancer-Tarceva administered concurrently with gemcitabine**

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

The most frequent ADRs in study PA.3 in pancreatic cancer patients receiving Tarceva 100 mg plus gemcitabine were fatigue, rash and diarrhoea. In the Tarceva plus gemcitabine arm, Grade 3/4 rash and diarrhoea were 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 Tarceva plus gemcitabine.

The Tarceva 150 mg plus gemcitabine cohort (23 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 Tarceva) and PA.3 (treated with Tarceva plus gemcitabine) studies and ADRs occurring more frequently (≥ 3%) than placebo in BR.21 (treated with Tarceva) and PA.3 (treated with Tarceva plus gemcitabine) studies

	Tarceva (BR.21) (n=485)			**Tarceva (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							
Infections*	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							
Conjunctivitis	12	< 1	0	--	--	--	*very common*
Keratocojunctivitis sicca	12	0	0	--	--	--	*very common*
Psychiatric disorders							
Depression	--	--	--	19	2	0	*very common*
Nervous system disorders							
Headache	--	--	--	15	< 1	0	*very common*
Neuropathy	--	--	--	13	1	< 1	*very common*
Respiratory, thoracic and mediastinal disorders							
Dyspnea	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*

*Severe infection, with or without neutropenia, have included pneumonia, sepsis and cellulites.
-- corresponds to percentage below threshold

Further information on ADRs of special interest

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

Very common ADRs are presented in Table 1, ADRs in other frequency categories are summarized below.

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

Case of gastrointestinal bleeding have been reported commonly (including some fatalities), some associated with concomitant warfarin administration (see also section *2.8 Interactions with Other Medicinal Products and Other Forms of Interaction*) and some with concomitant NSAID.

Hepato-biliary disorders:
Liver function test abnormalities (including raised alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin) have been observed commonly in clinical trials of Tarceva. In study PA.3, 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 Tarceva. Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medications (see section *2.4 Warnings and Precautions*).

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

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 Tarceva for treatment of NSCLC or other advanced solid tumours (see section *2.4 Warnings and Precautions*).

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

Skin and subcutaneous tissue orders:
Rash has been reported very commonly in patients receiving Tarceva and in general, 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 sun screen (e.g., mineral-containing) may be advisable. Acne, dermatitis acneiform and folliculitis have been observed commonly, most of these events were mild or moderate and non-serious. 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.

2.6.2 Postmarketing Experience

The following adverse drug reactions have been identified from postmarketing experience with Tarceva 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

2.7 Overdose

Single oral doses of Tarceva up to 1000 mg erlotinib in healthy subjects, and up to 1600 mg given as a single dose once weekly 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 diarrhoea, rash and possibly liver transaminase elevation may occur above the recommended dose. In case of suspected overdose, Tarceva should be withheld and symptomatic treatment administrated.

2.8 Interactions with Other Medicinal 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, and the pulmonary isoform CYP1A1. Potential interactions may occur with drugs 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. Inhibition of CYP3A4 metabolism by ketoconazole (200 mg orally twice daily for 5 days) resulted in an increase exposure to erlotinib (86% in median erlotinib exposure [AUC]) and 69% in C_{max} when compared to erlotinib alone. When Tarceva was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2, the erlotinib exposure [AUC] and

maximum concentration (C_{max}) increased by 39% and 17%, respectively. Therefore, caution should be used when administering Tarceva with potent CYP3A4 or combined CYP3A4/CYP1A2 inhibitors. In these situations, the dose of Tarceva 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 orally once daily for 7 days) resulted in a 69% decrease in the median erlotinib AUC, following a 150 mg dose of Tarceva as compared to Tarceva alone.

Pre-treatment and co-administration of rifampicin with a single 450 mg dose of Tarceva resulted in a mean erlotinib exposure [AUC] of 57.5% of that after a single 150 mg Tarceva 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 Tarceva and a potent CYP3A4 inducer such as rifampicin an increase in dose to 300 mg should be considered while their safety (see section *2.4.1 Warnings and Precautions, General*) 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.

Pre-treatment or co-administration of Tarceva 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.

The solubility of erlotinib is pH dependent. Erlotinib solubility decreases as pH increases. Drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and hence its bioavailability. Co-administration of Tarceva with omeprazole, a proton pump inhibitor, decreased the erlotinib exposure [AUC] and C_{max} by 46% and 61%, respectively. There was no change to T_{max} or half-life. Concomitant administration of Tarceva with 300 mg ranitidine, an H_2-receptor antagonist, decreased erlotinib exposure [AUC] and C_{max} by 33% and 54%, respectively. Therefore, co-administration of drugs reducing gastric acid production with Tarceva should be avoided where possible. Increasing the dose of Tarceva when co-administered with such agents is not likely to compensate for this loss of exposure. However, when Tarceva was dosed in a staggered manner 2 hours before or 10 hours after ranitidine 150 mg b.i.d., erlotinib exposure [AUC] and C_{max} decreased only by 15% and 17%, respectively. If patients need to be treated with such drugs, then an H_2-receptor antagonist such as ranitidine should be considered and used in a staggered manner. Tarceva must be taken at least 2 hours before or 10 hours after the H_2-receptor antagonist dosing.

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

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

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 *2.2.1 Special Dosage Instructions, 3.2.5 Pharmacokinetics in Special Populations*).

Erlotinib is a substrate for the P-glycoprotein (Pgp) 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. The effect of antacids, proton pump inhibitors and H_2 antagonists on the absorption of erlotinib have not been investigated but absorption may be impaired, leading to lower plasma levels. Caution should be exercised when these medicinal products are combined with erlotinib.

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.

3. PHARMACOLOGICAL PROPERTIES AND EFFECT

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.

- ***Non-small cell lung cancer***

*Tarceva administered as monotherapy**:***

First-line therapy for patients with EGFR activating mutations:
The efficacy of Tarceva 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 Tarceva 150 mg or platinum based doublet chemotherapy.

The primary endpoint of investigator assessed progression free survival (PFS), was determined at a pre-planned interim analysis (n=153, hazard ratio (HR) = 0.42, 95% CI, 0.27 to 0.64; $p < 0.0001$ for the Tarceva 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 Tarceva versus chemotherapy arms respectively, median PFS was 9.4 and 5.2 months and objective response rate (ORR) was 54.5% and 10.5%. PFS results were confirmed by an independent review of the scans, median PFS was 10.4 months in the Tarceva group compared with 5.4 months in the chemotherapy group (HR=0.47, 95% CI, 0.27 to 0.78; p=0.003). 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).

At an updated analysis with 62% of OS maturity, OS HR was 0.93 (95% CI, 0.64 to 1.36, p=0.7149). 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 Tarceva. In the updated analysis, PFS results remained consistent with the interim analysis results. Median PFS assessed by the investigators was 10.4 and 5.1 months in the Tarceva and chemotherapy arms respectively (HR = 0.34, 95% CI, 0.23 to 0.49, $p < 0.0001$).

- *Additional published data*

In a prospective analysis of patients with advanced NSCLC having tumours with activating mutations in the EGFR TK domain, the median PFS for the 113 patients treated with first-line Tarceva was 14 months (95% CI, 9.7 to 18.3 months) and the median overall survival was 28.0 months (95% CI, 22.7 to 33 months).

A pooled analysis of published data from NSCLC patients showed that patients having tumours with EGFR activating mutations and receiving Tarceva as predominantly first-line therapy (n=70, 12.5 months, 95% CI [10.6-16.0]) had a longer median PFS compared to those receiving chemotherapy (n=359, 6.0 months, 95% CI [5.4-6.7]).

Second/Third-line therapy:

The efficacy and safety of Tarceva in second/third-line therapy of NSCLC was demonstrated in a randomized, double-blind, placebo-controlled trial (BR.21). 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 randomized 2:1 to receive Tarceva 150 mg or placebo orally once daily. Study endpoints included overall survival, time to deterioration of lung cancer-related symptoms (cough, dyspnoea and pain), response rate, duration of response, progression-free survival (PFS), and safety. The primary end-point was survival.

Due to the 2:1 randomization, 488 patients were randomized to Tarceva and 243 patients to placebo. Patients were not selected for HER1/EGFR status, gender, race, smoking history and histological 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 Tarceva 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 Tarceva 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 randomization (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 Tarceva 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.

The survival benefit with Tarceva treatment was seen across most subsets. A series of subsets of patients formed by the values of the stratification factors at randomization and at baseline, HER1/EGFR status, prior exposure to taxanes, smoking history, gender, age, histology, prior weight loss, time between initial diagnosis and randomization, and geographic location were examined in exploratory univariate analyses to assess the robustness of the overall survival result. Nearly all of the hazard ratios in the Tarceva group relative to the placebo group were less than 1.0, suggesting that the survival benefit from Tarceva was robust across subsets. Of note, the survival benefit of Tarceva was comparable in patients with a baseline ECOG PS of 2-3 (HR=0.77) or a PS of 0-1

(HR=0.73) and patients who had received one chemotherapy regimen (HR=0.76) or two or more regimens (HR=0.76).

A survival benefit of Tarceva 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 0.83 among patients whose best response was stable disease and 0.85 among patients whose best response was progressive disease.

Table 3 summarizes the results for the study, including survival, time to deterioration of lung cancer-related symptoms, and progression-free survival (PFS).

Table 3 Study BR.21 Efficacy Results

	Tarceva (n=488)	Placebo (n=243)	p-value
Median survival 95% CI	6.7 months (5.5 to 7.8)	4.7 months (4.1 to 6.3)	
Difference between survival curves			0.001
Hazard ratio*, mortality (erlotinib: placebo) 95% CI (risk ratio)	0.73 0.60 to 0.87		
Median time to deterioration in cough*** 95% CI	28.1 weeks (16.1 to 40.0)	15.7 weeks (9.3 to 24.3)	0.041
Median time to deterioration in dyspnea*** 95% CI	20.4 weeks (16.3 to 28.3)	12.1 weeks (9.3 to 20.9)	0.031**
Median time to deterioration in pain*** 95% CI	12.1 weeks (10.1 to 14.1)	8.1 weeks (7.7 to 12.3)	0.040**
Median progression-free survival 95% CI	9.7 weeks (8.4 to 12.4)	8.0 weeks (7.9 to 8.0)	< 0.001

*Adjusted for stratification factors and HER1/EGFR status; a value less than 1.00 favors Tarceva (primary analysis).

**p-value adjusted for multiple testing.

***From the EORTC QLQ-C30 and QLQ-LC13 Quality of Life Questionnaire.

Symptom deterioration was measured using the EORTC QLQ-C30 and QLQ-LC13 quality of life questionnaires. Baseline scores of cough, dyspnea and pain were similar in the two treatment groups. Tarceva resulted in symptom benefits by significantly prolonging time to deterioration in cough (HR=0.75), dyspnea (HR=0.72) and pain (HR=0.77), versus placebo. These symptom benefits were not due to an increased use of palliative radiotherapy or concomitant medication in the Tarceva group.

The median PFS was 9.7 weeks in the Tarceva 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 Tarceva and placebo arms.

The objective response rate by RECIST in the Tarceva 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 Tarceva and placebo groups (p=0.004).

- **Pancreatic cancer** *(Tarceva administered concurrently with gemcitabine):*

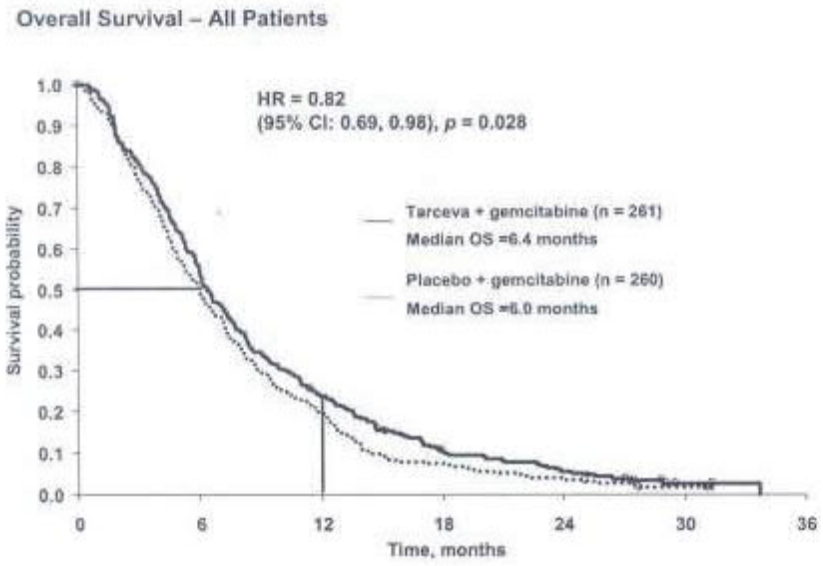
The efficacy and safety of Tarceva in combination with gemcitabine as a first-line treatment was assessed in a randomized, double blind, placebo-controlled trial in 569 patients with locally advanced, unresectable or metastatic pancreatic cancer. Patients were randomized 1:1 to receive Tarceva (100 mg or 150 mg) or placebo once daily on a continuous schedule plus gemcitabine IV (1000 mg/m^2, 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]). Tarceva or placebo was taken orally once daily until disease progression or unacceptable toxicity. Study end points included overall survival, response rate and PFS. Duration of response was also examined. The primary endpoint was survival. A total of 285 patients were randomized to receive gemcitabine plus Tarceva (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.

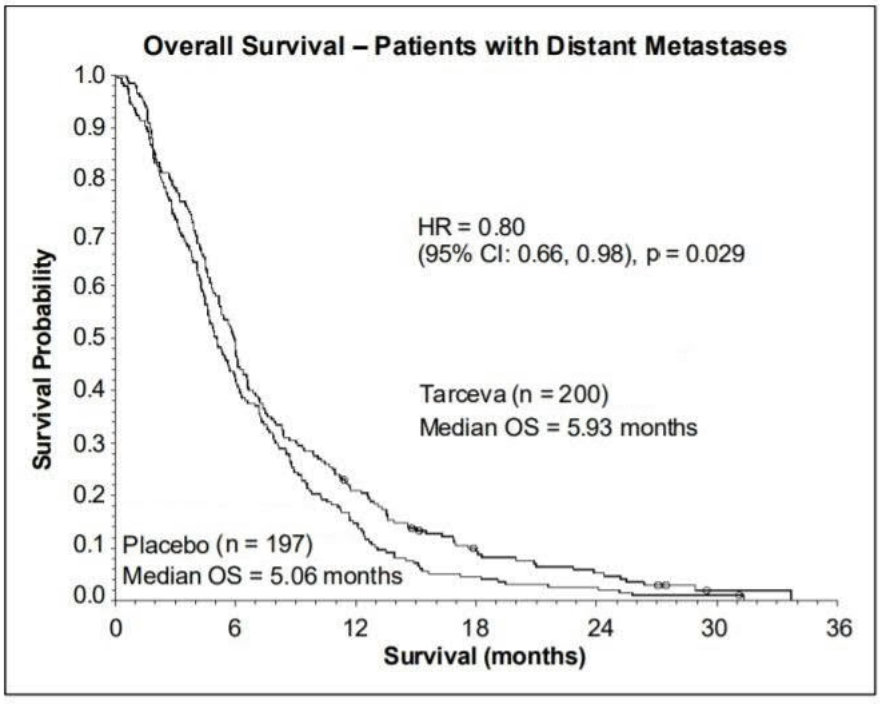
Baseline demographic and disease characteristics of the patients were similar between the 2 treatment groups, 100 mg Tarceva plus gemcitabine or placebo plus gemcitabine, except for a slightly larger proportion of females in the Tarceva arm (51%) compared with the placebo arm (44%). The median time from 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 Tarceva 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 Tarceva 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 Tarceva group compared to 19.4% in the placebo group. The median overall survival was 6.4 months in the Tarceva group compared with 6 months in the placebo group.
Table 4 summarizes the results of the study.

Table 4 Study PA3 Efficacy Results

	Tarceva 100 mg 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 Tarceva 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 Tarceva 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 Tarceva and placebo groups (p=0.036).

3.1.3 Immunogenicity
Not applicable.

3.2 PHARMACOKINETIC PROPERTIES
Exposure:
Following a 150 mg oral dose of Tarceva, at steady state, the median time to reach maximum plasma concentrations is approximately 4.0 hours with median maximum plasma concentrations achieved of 1995 ng/mL. Prior to the next dose at 24 hours, the median minimum plasma concentrations are 1238 ng/mL Median AUC achieved during the dosing interval at steady state are 41.300 mcg*hr/mL.

3.2.1 Absorption
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 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 Tarceva, tumour samples from surgical excisions on Day 9 of treatment revealed tumour concentrations of erlotinib that averaged 1185 ng/g of tissue. This corresponded to an overall average of 63% of the steady state observed peak plasma concentrations. The primary active metabolites were present in tumour at concentrations averaging 160 ng/g tissue, which corresponded to an overall average of 113% of the observed steady state peak plasma concentrations. Tissue distribution studies using whole body autoradiography following oral administration with [^{14}C] labeled erlotinib in athymic nude mice with HN5 tumour 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 the hepatic cytochromes, primarily 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 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* tumour models. They are present in plasma at levels that are < 10% of erlotinib and display similar pharmacokinetics as erlotinib.

3.2.4 Elimination

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.

Clearance:

A population pharmacokinetic analysis in 591 patients receiving single agent Tarceva 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. (see *2.8 Interactions with Other Medicinal Products and Other Forms of Interaction*)

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.

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 $AUC_{0-\infty}$ in smokers was about 1/3 of that in never/former smokers (n=16 in each of smoker and never/former smoker arms). This reduced exposure in current smokers is presumably due to induction of CYP1A1 in lung and CYP1A2 in the liver.

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

Based on population pharmacokinetic analysis, no clinically significant relationship between predicted apparent clearance and patient age, bodyweight, gender and ethnicity were observed.

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

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 Tarceva 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) (see sections *2.2.1 Special Dosage Instructions*, *2.8 Interactions with Other Medicinal Products and Other Forms of Interaction*).

3.3 NONCLINICAL SAFETY DATA

3.3.1 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.

3.3.2 Genotoxicity

Erlotinib was negative in the standard battery of genotoxicity assays.

3.3.3 Impairment of Fertility

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

3.3.4 Reproductive Toxicology

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.

3.3.5 Others

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 diarrhoea). 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.

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

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

Stability

Do not store above 30°C.
Tarceva should not be used after the expiry date (EXP) shown on the pack.

Packs

Film-coated Tablet 100 mg

Box, 3 blisters @ 10 film-coated tablets Reg.No.: DKIXXXXXXXX

Film-coated Tablet 150 mg

Box, 3 blisters @ 10 film-coated tablets Reg.No.: DKIXXXXXXXX

Medicine: keep out of reach of children
On medical prescriptions only
Harus dengan resep dokter

Made for:
F. Hoffmann-La Roche Ltd, Basel, Switzerland
By Delpharm Milano S.r.l, Segrate, Italy

Imported by
PT Menarini Indria Laboratories
Bekasi, Indonesia

Distributed by:
PT Roche Indonesia
Jakarta, Indonesia

(This PI draft has been reviewed and approved for submission by Pramelita on 28-Apr-2021)