

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tarceva 25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tarceva 25 mg

One film-coated tablet contains 25 mg erlotinib (as erlotinib hydrochloride).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White to yellowish, round, biconvex tablets with 'Tarceva 25' and logo printed in brownish yellow on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-small cell lung cancer (NSCLC):

Tarceva is indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after 4 cycles of standard platinum-based first-line chemotherapy.

Tarceva is also 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 (see section 5.1).

Pancreatic cancer:

Tarceva in combination with gemcitabine is indicated for the treatment of patients with metastatic pancreatic cancer.

When prescribing Tarceva, factors associated with prolonged survival should be taken into account (see section 4.2 and 5.1).

No survival advantage could be shown for patients with locally advanced disease.

4.2 Posology and method of administration

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

Non-small cell lung cancer:

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 5.1).

When dose adjustment is necessary, reduce in 50 mg steps (see section 4.4).

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

Concomitant use of CYP3A4 substrates and modulators may require dose adjustment (see section 4.5).

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 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 (see section 5.2).

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 5.2). 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. Efficacy and long term safety of a dose higher than the recommended starting doses have not been established in patients who continue to smoke cigarettes (see sections 4.5 and 5.2). Therefore, current smokers should be advised to stop smoking, as plasma concentrations of erlotinib in smokers as compared to non-smokers are reduced.

4.3 Contraindications

Severe hypersensitivity to erlotinib or to any of the excipients.

4.4 Special warnings and precautions for use

Potent inducers of CYP3A4 may reduce the efficacy of erlotinib whereas potent inhibitors of CYP3A4 may lead to increased toxicity. Concomitant treatment with these types of agents should be avoided (see section 4.5).

Current smokers should be advised to stop smoking, as plasma concentrations of erlotinib in smokers as compared to non-smokers are reduced. The degree of reduction is likely to be clinically significant (see section 4.5).

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 ILD (0.8 %) was the same in both the placebo and Tarceva groups. 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. The overall incidence in Tarceva-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) is approximately 0.6 % compared to 0.2 % in patients on placebo. Reported diagnoses in patients suspected of having ILD-like events included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease,

obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome (ARDS), alveolitis, and lung infiltration. Symptoms started from a few days to several months after initiating Tarceva therapy. Confounding or contributing factors such as concomitant or prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections were frequent.

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 4.8).

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 4.8). 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), 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.

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 4.8). Tarceva is not recommended for use in patients with severe hepatic dysfunction.

Patients receiving Tarceva are at increased risk of developing gastrointestinal perforation, which was observed uncommonly. 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 4.8).

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 4.8). Tarceva treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions.

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 4.8).

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.

Erlotinib is characterised by a decrease in solubility at pH above 5. Drugs that alter the pH of the upper GI tract, like proton pump inhibitors, H₂ antagonists and antacids, may alter the solubility of erlotinib and hence its bioavailability. Increasing the dose of Tarceva when coadministered with such agents is not likely to compensate for the loss of exposure. Combination of erlotinib with proton pump inhibitors should be avoided. The effects of concomitant administration of erlotinib with H₂

antagonists and antacids are unknown; however, reduced bioavailability is likely. Therefore, concomitant administration of these combinations should be avoided (see section 4.5). If the use of antacids is considered necessary during treatment with Tarceva, they should be taken at least 4 hours before or 2 hours after the daily dose of Tarceva.

4.5 Interaction 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.

When erlotinib was co-administered with ciprofloxacin, a moderate CYP1A2 inhibitor, the erlotinib exposure [AUC] increased significantly by 39 %, while no statistically significant change in C_{max} was found. Similarly, the exposure to the active metabolite increased by about 60% and 48% for AUC and C_{max} , respectively. The clinical relevance of this increase has not been established. Caution should be exercised when ciprofloxacin or potent CYP1A2 inhibitors (e.g. fluvoxamine) are combined with erlotinib. If adverse events related to erlotinib are observed, the dose of erlotinib may be reduced.

Pretreatment or coadministration of Tarceva did not alter the clearance of the prototypical CYP3A4 substrates, midazolam and erythromycin, but did appear to decrease the oral bioavailability of midazolam by up to 24%. In another clinical study, erlotinib was shown not to affect pharmacokinetics of the concomitantly administered CYP3A4/2C8 substrate paclitaxel. Significant interactions with the clearance of other CYP3A4 substrates are therefore unlikely.

The inhibition of glucuronidation may cause interactions with medicinal products which are substrates of UGT1A1 and exclusively cleared by this pathway. Patients with low expression levels of UGT1A1 or genetic glucuronidation disorders (e.g. Gilbert's disease) may exhibit increased serum concentrations of bilirubin and must be treated with caution.

Erlotinib is metabolised in the liver by the hepatic cytochromes in humans, primarily CYP3A4 and to a lesser extent by CYP1A2. Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung, and CYP1B1 in tumour tissue also potentially contribute to the metabolic clearance of erlotinib. Potential interactions may occur with active substances which are metabolised by, or are inhibitors or inducers of, these enzymes.

Potent inhibitors of CYP3A4 activity decrease erlotinib metabolism and increase erlotinib plasma concentrations. 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 % of AUC and 69 % of C_{max}). Therefore, caution should be used when erlotinib is combined with a potent CYP3A4 inhibitor, e.g.azole antifungals (i.e. ketoconazole, itraconazole, voriconazole), protease inhibitors, erythromycin or clarithromycin. If necessary the dose of erlotinib should be reduced, particularly if toxicity is observed.

Potent inducers of CYP3A4 activity increase erlotinib metabolism and significantly decrease erlotinib plasma concentrations. In a clinical study, the concomitant use of erlotinib and rifampicin (600 mg orally once daily for 7 days), a potent CYP3A4 inducer, resulted in a 69 % decrease in the median erlotinib AUC. 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. Co-administration of Tarceva with CYP3A4 inducers should therefore be avoided. 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 (including renal and liver functions and serum electrolytes) is closely monitored, and if well tolerated for more than 2 weeks, further increase to 450 mg could be considered with close safety monitoring. Reduced exposure may also occur with other inducers e.g. phenytoin, carbamazepine, barbiturates or St. Johns

Wort (*hypericum perforatum*). Caution should be observed when these active substances are combined with erlotinib. Alternate treatments lacking potent CYP3A4 inducing activity should be considered when possible.

International Normalized Ratio (INR) elevations, and bleeding events including gastrointestinal bleeding have been reported in clinical studies, some associated with concomitant warfarin administration (see section 4.8) and some with concomitant NSAID administration. Patients taking warfarin or other coumarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR.

Results of a pharmacokinetic interaction study indicated a significant 2.8-, 1.5- and 9-fold reduced AUC_{inf} , C_{max} and plasma concentration at 24 hours, respectively, after administration of Tarceva in smokers as compared to non-smokers (see section 5.2). Therefore, patients who are still smoking should be encouraged to stop smoking as early as possible before initiation of treatment with Tarceva, 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 (PPI), decreased the erlotinib exposure [AUC] and maximum concentration [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 H₂-receptor antagonist, decreased erlotinib exposure [AUC] and maximum concentrations [C_{max}] by 33% and 54%, respectively. 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 maximum concentrations [C_{max}] decreased only by 15% and 17%, respectively. The effect of antacids on the absorption of erlotinib have not been investigated but absorption may be impaired, leading to lower plasma levels. In summary, the combination of erlotinib with proton pump inhibitors should be avoided. If the use of antacids is considered necessary during treatment with Tarceva, they should be taken at least 4 hours before or 2 hours after the daily dose of Tarceva. If the use of ranitidine is considered, it should be used in a staggered manner; i.e. Tarceva must be taken at least 2 hours before or 10 hours after ranitidine dosing.

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 AUC_{0-48} 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 C_{max} 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.

4.6 Pregnancy and lactation

There are no studies in pregnant women using erlotinib. Studies in animals have shown some reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Women of childbearing potential must be advised to avoid pregnancy while on Tarceva. Adequate contraceptive methods should be used during therapy, and for at least 2 weeks after completing therapy. Treatment should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the foetus.

It is not known whether erlotinib is excreted in human milk. Because of the potential harm to the infant, mothers should be advised against breastfeeding while receiving Tarceva.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Non-small cell lung cancer (Tarceva administered as monotherapy):

In a randomized double-blind study (BR.21; Tarceva administered as second line therapy), rash (75 %) and diarrhoea (54 %) were the most commonly reported adverse drug reactions (ADRs). Most were Grade 1/2 in severity and manageable without intervention. Grade 3/4 rash and diarrhoea occurred in 9 % and 6 %, respectively in Tarceva-treated patients and each resulted in study discontinuation in 1 % of patients. Dose reduction for rash and diarrhoea was needed in 6 % and 1 % of patients, respectively. In study BR.21, the median time to onset of rash was 8 days, and the median time to onset of diarrhoea was 12 days.

In general, rash manifests as a mild or moderate erythematous and papulopustular rash, which may occur or worsen in sun exposed areas. For patients who are exposed to sun, protective clothing, and/or use of sun screen (e.g. mineral-containing) may be advisable.

Adverse events occurring more frequently (≥ 3 %) in Tarceva-treated patients than in the placebo group in the pivotal study BR.21, and in at least 10 % of patients in the Tarceva group, are summarised by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Grade in Table 1.

Table 1: Very common ADRs in study BR.21

NCI-CTC Grade	Erlotinib N = 485			Placebo N = 242		
	Any Grade	3	4	Any Grade	3	4
MedDRA Preferred Term	%	%	%	%	%	%
Total patients with any AE	99	40	22	96	36	22
<i>Infections and infestations</i>						
Infection*	24	4	0	15	2	0
<i>Metabolism and nutrition disorders</i>						
Anorexia	52	8	1	38	5	<1
<i>Eye disorders</i>						
Conjunctivitis	12	<1	0	2	<1	0
Keratoconjunctivitis sicca	12	0	0	3	0	0

NCI-CTC Grade	Erlotinib N = 485			Placebo N = 242		
	Any Grade	3	4	Any Grade	3	4
MedDRA Preferred Term	%	%	%	%	%	%
<i>Respiratory, thoracic and mediastinal disorders</i>						
Dyspnoea	41	17	11	35	15	11
Cough	33	4	0	29	2	0
<i>Gastrointestinal disorders</i>						
Diarrhoea**	54	6	<1	18	<1	0
Nausea	33	3	0	24	2	0
Vomiting	23	2	<1	19	2	0
Stomatitis	17	<1	0	3	0	0
Abdominal pain	11	2	<1	7	1	<1
<i>Skin and subcutaneous tissue disorders</i>						
Rash***	75	8	<1	17	0	0
Pruritus	13	<1	0	5	0	0
Dry skin	12	0	0	4	0	0
<i>General disorders and administration site conditions</i>						
Fatigue	52	14	4	45	16	4

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

** Can lead to dehydration, hypokalemia and renal failure.

*** Rash included dermatitis acneiform.

In another double-blind, randomized, placebo-controlled Phase III study BO18192 (SATURN); Tarceva was administered as maintenance after first-line chemotherapy. SATURN was conducted in 889 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 Tarceva in study BO18192 were rash and diarrhoea (any Grade 49% and 20%, respectively), most were Grade 1/2 in severity and manageable without intervention. Grade 3 rash and diarrhoea occurred in 6% and 2% of patients, respectively. No Grade 4 rash or diarrhoea was observed. Rash and diarrhoea resulted in discontinuation of Tarceva in 1% and <1% of patients, respectively. Dose modifications (interruptions or reductions) for rash and diarrhoea were needed in 8.3% and 3% of patients, respectively.

Pancreatic cancer (Tarceva administered concurrently with gemcitabine):

The most common adverse reactions in pivotal 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 each reported in 5 % of patients. The median time to onset of rash and diarrhoea was 10 days and 15 days, respectively. Rash and diarrhoea each resulted in dose reductions in 2 % of patients, and resulted in study discontinuation in up to 1 % of patients receiving Tarceva plus gemcitabine.

Adverse events occurring more frequently (≥ 3 %) in Tarceva 100 mg plus gemcitabine-treated patients than in the placebo plus gemcitabine group in the pivotal study PA.3, and in at least 10 % of patients in the Tarceva 100 mg plus gemcitabine group, are summarised by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Grade in Table 2.

Table 2: Very common ADRs in study PA.3 (100 mg cohort)

NCI-CTC Grade	Erlotinib N = 259			Placebo N = 256		
	Any Grade	3	4	Any Grade	3	4
MedDRA Preferred Term	%	%	%	%	%	%
Total patients with any AE	99	48	22	97	48	16
<i>Infections and infestations</i>						
Infection*	31	3	<1	24	6	<1
<i>Metabolism and nutrition disorders</i>						
Weight decreased	39	2	0	29	<1	0
<i>Psychiatric disorders</i>						
Depression	19	2	0	14	<1	0
<i>Nervous system disorders</i>						
Headache	15	<1	0	10	0	0
Neuropathy	13	1	<1	10	<1	0
<i>Respiratory, thoracic and mediastinal disorders</i>						
Cough	16	0	0	11	0	0
<i>Gastrointestinal disorders</i>						
Diarrhoea**	48	5	<1	36	2	0
Stomatitis	22	<1	0	12	0	0
Dyspepsia	17	<1	0	13	<1	0
Flatulence	13	0	0	9	<1	0
<i>Skin and subcutaneous tissue disorders</i>						
Rash***	69	5	0	30	1	0
Alopecia	14	0	0	11	0	0
<i>General disorders and administration site conditions</i>						
Pyrexia	36	3	0	30	4	0
Fatigue	73	14	2	70	13	2
Rigors	12	0	0	9	0	0

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

** Can lead to dehydration, hypokalemia and renal failure.

*** Rash included dermatitis acneiform.

Other Observations:

Safety evaluation of 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 or 150 mg in combination with gemcitabine.

The following terms are used to rank the undesirable effects by frequency: very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1000); very rare (<1/10,000) including isolated reports.

The following adverse reactions have been observed in patients who received Tarceva administered as single agent and patients who received Tarceva concurrently with chemotherapy.

Very common ADR's are presented in Tables 1 and 2, ADR's in other frequency categories are summarized below.

Gastrointestinal disorders:

Common: Gastrointestinal bleeding. In clinical studies, some cases have been associated with concomitant warfarin administration (see section 4.5) and some with concomitant NSAID administration.

Uncommon: Gastrointestinal perforations.

Skin and subcutaneous tissue disorders:

Common: Alopecia.

Common (in PA.3): Dry skin.

Common: Paronychia.

Uncommon: Hirsutism, eyebrow changes and brittle and loose nails.

Uncommon: Mild skin reactions such as hyperpigmentation.

Very rare: Cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal.

Hepato-biliary disorders:

Very common (in PA.3)

Common (in BR.21): Liver function test abnormalities (including increased alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). These were mainly mild or moderate in severity, transient in nature or associated with liver metastases.

Rare: 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 4.4).

Eye disorders:

Common: Keratitis.

Common: Conjunctivitis in study PA.3.

Uncommon: Eyelash changes (including in-growing eyelashes, excessive growth and thickening of the eyelashes).

Very rare: Corneal ulcerations and perforations.

Respiratory, thoracic and mediastinal disorders:

Common: Epistaxis.

Uncommon: Serious interstitial lung disease (ILD), including fatalities, in patients receiving Tarceva for treatment of NSCLC or other advanced solid tumours (see section 4.4).

4.9 Overdose

Single oral doses of Tarceva up to 1000 mg erlotinib 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 diarrhoea, rash and possibly increased activity of liver aminotransferases may occur above the recommended dose. In case of suspected overdose, Tarceva should be withheld and symptomatic treatment initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agent, ATC code: L01XE03

Erlotinib is an epidermal growth factor receptor/human epidermal growth factor receptor type 1 (EGFR also known as HER1) tyrosine kinase inhibitor. Erlotinib potently inhibits the intracellular phosphorylation of EGFR. EGFR is expressed on the cell surface of normal cells and cancer cells. In non-clinical models, inhibition of EGFR phosphotyrosine results in cell stasis and/or death.

Non-small cell lung cancer (Tarceva administered as monotherapy):

Maintenance after first-line chemotherapy:

The efficacy and safety of Tarceva as maintenance after first-line chemotherapy for NSCLC was demonstrated 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 after 4 cycles of platinum-based doublet chemotherapy. Patients were randomized 1:1 to receive Tarceva 150 mg or placebo orally once daily until disease progression. The primary endpoint of the study was progression free survival (PFS) in all patients and in patients with an EGFR IHC positive tumour. Baseline demographic and disease characteristics were well balanced between the two treatment arms. Patients with ECOG PS>1, significant hepatic or renal co-morbidities were not included in the study.

- ITT population results:

The primary PFS analysis in all patients (n=889) showed a PFS hazard ratio (HR) of 0.71 (95 % CI, 0.62 to 0.82; p<0.0001) for the Tarceva group relative to the placebo group. The mean PFS was 22.4 weeks in the Tarceva group compared with 16.0 weeks in the placebo group. PFS results were confirmed by an independent review of the scans. Quality of life data did not suggest a detrimental effect from erlotinib compared with placebo.

A PFS HR of 0.69 (95% CI, 0.58 to 0.82; p < 0.0001) was observed in the coprimary patient population with EGFR IHC positive tumours (n=621). The mean PFS was 22.8 weeks in the Tarceva group (range 0.1 to 78.9 weeks) compared with 16.2 weeks in the placebo group (range 0.1 to 88.1 weeks). The progression free survival rate at 6 months was 27% and 16%, respectively for Tarceva and placebo.

Concerning the secondary endpoint of overall survival, the HR was 0.81 (95% CI, 0.70 to 0.95; p=0.0088). The median overall survival was 12.0 months in the Tarceva group versus 11.0 months in the placebo group.

Patients with EGFR activating mutations had the largest benefit (n= 49, PFS HR=0.10, 95 % CI, 0.04 to 0.25; p<0.0001). In patients with EGFR wild type tumours (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).

- Patients with Stable Disease after chemotherapy:

Patients with stable disease (SD) (n= 487) had a PFS HR of 0.68 (95% CI, 0.56 to 0.83; p<0.0001; median 12.1 weeks in the Tarceva group and 11.3 weeks in the placebo group) and an overall survival HR of 0.72 (95% CI, 0.59 to 0.89; p= 0.0019; median 11.9 months in the Tarceva group and 9.6 months in the placebo group).

The effect on overall survival was explored across different subsets of patients with SD receiving Tarceva. This did not show major qualitative differences between patients with squamous cell carcinoma (HR 0.67, 95% CI, 0.48-0.92) and non-squamous cell carcinoma (HR 0.76, 95% CI 0.59-1.00) and between patients with EGFR activating mutations (HR 0.48, 95% 0.14-1.62) and without EGFR activating mutations (HR 0.65, 95% CI 0.48-0.87).

Treatment after failure of at least one prior chemotherapy regimen:

The efficacy and safety of Tarceva as second/third-line therapy was demonstrated in a randomised, double-blind, placebo-controlled trial (BR.21), in 731 patients with locally advanced or metastatic NSCLC after failure of at least one chemotherapy regimen. Patients were randomised 2:1 to receive Tarceva 150 mg or placebo orally once daily. Study endpoints included overall survival,

progression-free survival (PFS), response rate, duration of response, time to deterioration of lung cancer-related symptoms (cough, dyspnoea and pain), and safety. The primary endpoint was survival.

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

The adjusted hazard ratio (HR) 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 percent of patients alive at 12 months was 31.2 % and 21.5 %, for the Tarceva and placebo groups, respectively. The median overall survival was 6.7 months in the Tarceva group (95 % CI, 5.5 to 7.8 months) compared with 4.7 months in the placebo group (95 % CI, 4.1 to 6.3 months).

The effect on overall survival was explored across different patient subsets. The effect of Tarceva 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, 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, 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, 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).

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

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

The objective response rate by RECIST in the Tarceva group was 8.9 % (95 % CI, 6.4 to 12.0).

The first 330 patients were centrally assessed (response rate 6.2 %); 401 patients were investigator-assessed (response rate 11.2 %).

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

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 0.82 (95 % CI, 0.68 to 0.99) among patients whose best response was stable disease or progressive disease.

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

Pancreatic cancer (Tarceva administered concurrently with gemcitabine in study PA.3):

The efficacy and safety of Tarceva in combination with gemcitabine as a first-line treatment was assessed in a randomised, double-blind, placebo-controlled trial in patients with locally advanced, unresectable or metastatic pancreatic cancer. Patients were randomised to receive Tarceva or placebo once daily on a continuous schedule plus gemcitabine IV (1000 mg/m², Cycle 1 - Days 1, 8, 15, 22, 29, 36 and 43 of an 8 week cycle; Cycle 2 and subsequent cycles - Days 1, 8 and 15 of a 4 week cycle

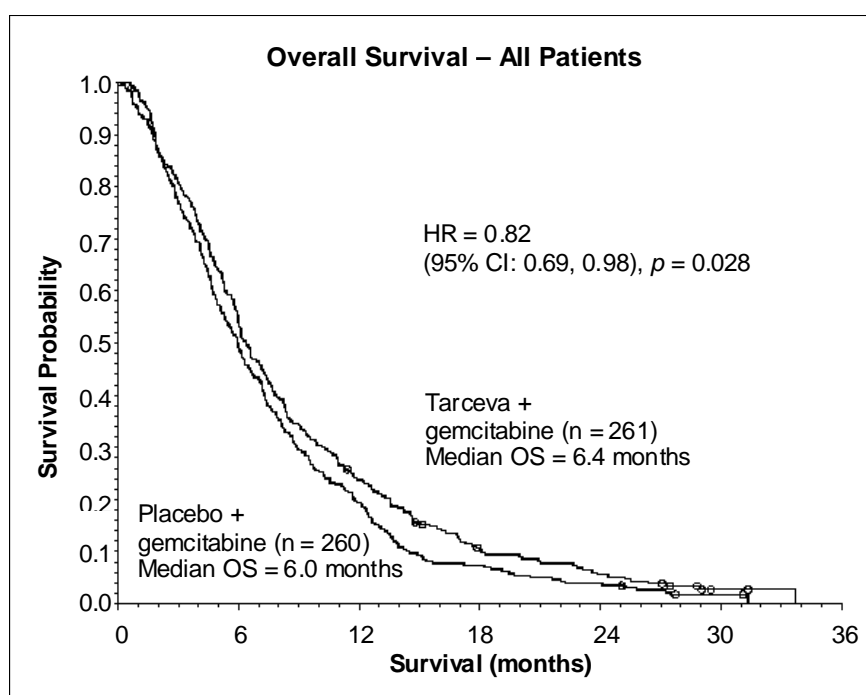
[approved dose and schedule for pancreatic cancer, see the gemcitabine SPC]). Tarceva or placebo was taken orally once daily until disease progression or unacceptable toxicity. The primary endpoint was overall survival.

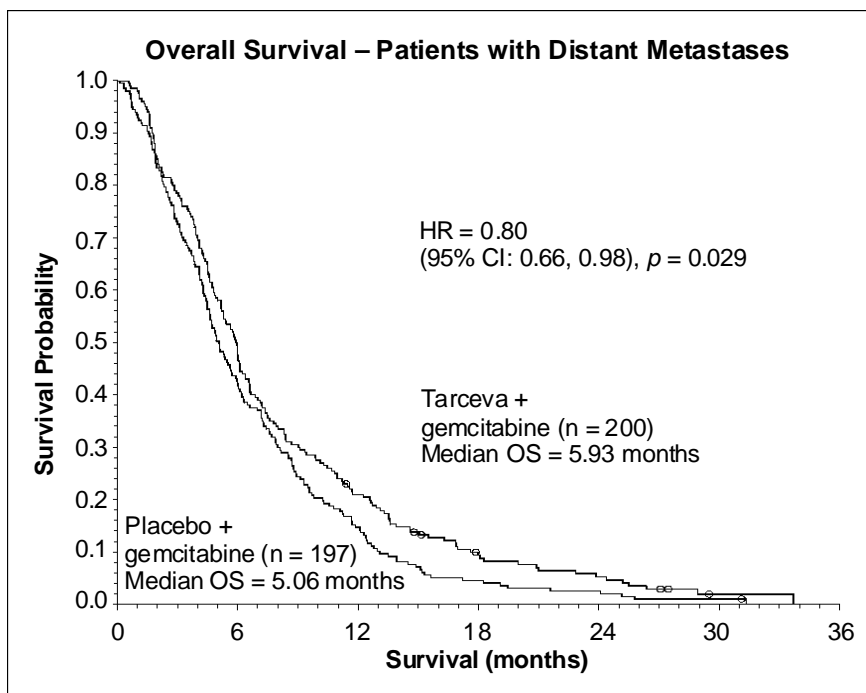
Baseline demographic and disease characteristics of the patients were similar between the 2 treatment groups, 100 mg Tarceva plus gemcitabine or placebo plus gemcitabine, except for a slightly larger proportion of females in the erlotinib/gemcitabine arm compared with the placebo/gemcitabine arm:

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

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

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





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

In a post-hoc analysis, patients on Tarceva who developed a rash had a longer overall survival compared to patients who did not develop rash (median OS 7.2 months vs 5 months, HR:0.61). 90% of patients on Tarceva developed rash within the first 44 days. The median time to onset of rash was 10 days.

5.2 Pharmacokinetic properties

Absorption: After oral administration, erlotinib peak plasma levels are obtained in approximately 4 hours after oral dosing. A study in normal healthy volunteers provided an estimate of the absolute bioavailability of 59 %. The exposure after an oral dose may be increased by food.

Distribution: Erlotinib has a mean apparent volume of distribution of 232 l and distributes into tumour tissue of humans. In a study of 4 patients (3 with non-small cell lung cancer [NSCLC], and 1 with laryngeal cancer) receiving 150 mg daily oral doses of Tarceva, tumour samples from surgical excisions on Day 9 of treatment revealed tumour concentrations of erlotinib that averaged 1,185 ng/g of tissue. This corresponded to an overall average of 63 % (range 5-161 %) of the steady state observed peak plasma concentrations. The primary active metabolites were present in tumour at concentrations averaging 160 ng/g tissue, which corresponded to an overall average of 113 % (range 88-130 %) of the observed steady state peak plasma concentrations. Plasma protein binding is approximately 95 %. Erlotinib binds to serum albumin and alpha-1 acid glycoprotein (AAG).

Metabolism: Erlotinib is metabolised in the liver by the hepatic cytochromes in humans, primarily CYP3A4 and to a lesser extent by CYP1A2. Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung, and 1B1 in tumour tissue potentially contribute to the metabolic clearance of erlotinib.

There are three main metabolic pathways identified: 1) O-demethylation of either side chain or both, followed by oxidation to the carboxylic acids; 2) oxidation of the acetylene moiety followed by hydrolysis to the aryl carboxylic acid; and 3) aromatic hydroxylation of the phenyl-acetylene moiety. The primary metabolites OSI-420 and OSI-413 of erlotinib produced by O-demethylation of either side chain have comparable potency to erlotinib in non-clinical *in vitro* assays and *in vivo* tumour

models. They are present in plasma at levels that are <10 % of erlotinib and display similar pharmacokinetics as erlotinib.

Elimination: Erlotinib is excreted predominantly as metabolites via the faeces (>90 %) with renal elimination accounting for only a small amount (approximately 9 %) of an oral dose. Less than 2 % of the orally administered dose is excreted as parent substance. A population pharmacokinetic analysis in 591 patients receiving single agent Tarceva shows a mean apparent clearance of 4.47 l/hour with a median half-life of 36.2 hours. Therefore, the time to reach steady state plasma concentration would be expected to occur in approximately 7-8 days.

Pharmacokinetics in special populations:

Based on population pharmacokinetic analysis, no clinically significant relationship between predicted apparent clearance and patient age, bodyweight, gender and ethnicity were observed. Patient factors, which correlated with erlotinib pharmacokinetics, were serum total bilirubin, AAG and current smoking. Increased serum concentrations of total bilirubin and AAG concentrations were associated with a reduced erlotinib clearance. The clinical relevance of these differences is unclear. However, smokers had an increased rate of erlotinib clearance. This was confirmed in a pharmacokinetic study in non-smoking and currently cigarette smoking healthy subjects receiving a single oral dose of 150 mg erlotinib. The geometric mean of the C_{max} was 1056 ng/mL in the non-smokers and 689 ng/mL in the smokers with a mean ratio for smokers to non-smokers of 65.2 % (95 % CI: 44.3 to 95.9, $p = 0.031$). The geometric mean of the AUC_{0-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 C_{24h} 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 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 ($n=17$).

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, the presence of an opioid appeared to increase exposure by about 11 %.

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 covariants 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.

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

Hepatic impairment: Erlotinib is primarily cleared by the liver. In patients with solid tumours and with moderately impaired hepatic function (Child-Pugh score 7-9), geometric mean erlotinib AUC_{0-t} and C_{max} was 27000 ng•h/mL and 805 ng/mL, respectively, as compared to 29300 ng•h/mL and 1090 ng/mL in patients with adequate hepatic function including patients with primary liver cancer or hepatic metastases. Although the C_{max} was statistically significant lower in moderately hepatic impaired patients, this difference is not considered clinically relevant. No data are available regarding the influence of severe hepatic dysfunction on the pharmacokinetics of erlotinib. In population

pharmacokinetic analysis, increased serum concentrations of total bilirubin were associated with a slower rate of erlotinib clearance.

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

5.3 Preclinical safety data

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

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

Erlotinib tested negative in conventional genotoxicity studies. Carcinogenicity studies have not been performed.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate
Cellulose, microcrystalline (E460)
Sodium starch glycolate Type A
Sodium laurilsulfate
Magnesium stearate (E470 b)

Tablet coat:

Hydroxypropyl cellulose (E463)
Titanium dioxide (E171)
Macrogol
Hypromellose (E464)

Printing ink yellow:

Shellac (E904)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC blister sealed with aluminium foil containing 30 tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/311/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 September 2005

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Tarceva 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tarceva 100 mg

One film-coated tablet contains 100 mg erlotinib (as erlotinib hydrochloride).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White to yellowish, round, biconvex tablets with 'Tarceva 100' and logo printed in grey on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-small cell lung cancer (NSCLC):

Tarceva is indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after 4 cycles of standard platinum-based first-line chemotherapy.

Tarceva is also 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 (see section 5.1).

Pancreatic cancer:

Tarceva in combination with gemcitabine is indicated for the treatment of patients with metastatic pancreatic cancer.

When prescribing Tarceva, factors associated with prolonged survival should be taken into account (see section 4.2 and 5.1).

No survival advantage could be shown for patients with locally advanced disease.

4.2 Posology and method of administration

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

Non-small cell lung cancer:

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 5.1).

When dose adjustment is necessary, reduce in 50 mg steps (see section 4.4).

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

Concomitant use of CYP3A4 substrates and modulators may require dose adjustment (see section 4.5).

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 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 (see section 5.2).

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 5.2). 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. Efficacy and long term safety of a dose higher than the recommended starting doses have not been established in patients who continue to smoke cigarettes (see sections 4.5 and 5.2). Therefore, current smokers should be advised to stop smoking, as plasma concentrations of erlotinib in smokers as compared to non-smokers are reduced.

4.3 Contraindications

Severe hypersensitivity to erlotinib or to any of the excipients.

4.4 Special warnings and precautions for use

Potent inducers of CYP3A4 may reduce the efficacy of erlotinib whereas potent inhibitors of CYP3A4 may lead to increased toxicity. Concomitant treatment with these types of agents should be avoided (see section 4.5).

Current smokers should be advised to stop smoking, as plasma concentrations of erlotinib in smokers as compared to non-smokers are reduced. The degree of reduction is likely to be clinically significant (see section 4.5).

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 ILD (0.8 %) was the same in both the placebo and Tarceva groups. 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. The overall incidence in Tarceva-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) is approximately 0.6 % compared to 0.2 % in patients on placebo. Reported diagnoses in patients suspected of having ILD-like events included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome (ARDS), alveolitis, and lung infiltration. Symptoms started from a few days to several months after initiating Tarceva therapy. Confounding or contributing factors such as concomitant or prior chemotherapy,

prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections were frequent.

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 4.8).

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 4.8). 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), 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.

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 4.8). Tarceva is not recommended for use in patients with severe hepatic dysfunction.

Patients receiving Tarceva are at increased risk of developing gastrointestinal perforation, which was observed uncommonly. 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 4.8).

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 4.8). Tarceva treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions.

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 4.8).

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.

Erlotinib is characterised by a decrease in solubility at pH above 5. Drugs that alter the pH of the upper GI tract, like proton pump inhibitors, H₂ antagonists and antacids, may alter the solubility of erlotinib and hence its bioavailability. Increasing the dose of Tarceva when coadministered with such agents is not likely to compensate for the loss of exposure. Combination of erlotinib with proton pump inhibitors should be avoided. The effects of concomitant administration of erlotinib with H₂ antagonists and antacids are unknown; however, reduced bioavailability is likely. Therefore, concomitant administration of these combinations should be avoided (see section 4.5). If the use of

antacids is considered necessary during treatment with Tarceva, they should be taken at least 4 hours before or 2 hours after the daily dose of Tarceva.

4.5 Interaction 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.

When erlotinib was co-administered with ciprofloxacin, a moderate CYP1A2 inhibitor, the erlotinib exposure [AUC] increased significantly by 39 %, while no statistically significant change in C_{max} was found. Similarly, the exposure to the active metabolite increased by about 60% and 48% for AUC and C_{max} , respectively. The clinical relevance of this increase has not been established. Caution should be exercised when ciprofloxacin or potent CYP1A2 inhibitors (e.g. fluvoxamine) are combined with erlotinib. If adverse events related to erlotinib are observed, the dose of erlotinib may be reduced.

Pretreatment or coadministration of Tarceva did not alter the clearance of the prototypical CYP3A4 substrates, midazolam and erythromycin, but did appear to decrease the oral bioavailability of midazolam by up to 24%. In another clinical study, erlotinib was shown not to affect pharmacokinetics of the concomitantly administered CYP3A4/2C8 substrate paclitaxel. Significant interactions with the clearance of other CYP3A4 substrates are therefore unlikely.

The inhibition of glucuronidation may cause interactions with medicinal products which are substrates of UGT1A1 and exclusively cleared by this pathway. Patients with low expression levels of UGT1A1 or genetic glucuronidation disorders (e.g. Gilbert's disease) may exhibit increased serum concentrations of bilirubin and must be treated with caution.

Erlotinib is metabolised in the liver by the hepatic cytochromes in humans, primarily CYP3A4 and to a lesser extent by CYP1A2. Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung, and CYP1B1 in tumour tissue also potentially contribute to the metabolic clearance of erlotinib. Potential interactions may occur with active substances which are metabolised by, or are inhibitors or inducers of, these enzymes.

Potent inhibitors of CYP3A4 activity decrease erlotinib metabolism and increase erlotinib plasma concentrations. 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 % of AUC and 69 % of C_{max}). Therefore, caution should be used when erlotinib is combined with a potent CYP3A4 inhibitor, e.g.azole antifungals (i.e. ketoconazole, itraconazole, voriconazole), protease inhibitors, erythromycin or clarithromycin. If necessary the dose of erlotinib should be reduced, particularly if toxicity is observed.

Potent inducers of CYP3A4 activity increase erlotinib metabolism and significantly decrease erlotinib plasma concentrations. In a clinical study, the concomitant use of erlotinib and rifampicin (600 mg orally once daily for 7 days), a potent CYP3A4 inducer, resulted in a 69 % decrease in the median erlotinib AUC. 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. Co-administration of Tarceva with CYP3A4 inducers should therefore be avoided. 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 (including renal and liver functions and serum electrolytes) is closely monitored, and if well tolerated for more than 2 weeks, further increase to 450 mg could be considered with close safety monitoring. Reduced exposure may also occur with other inducers e.g. phenytoin, carbamazepine, barbiturates or St. Johns Wort (*hypericum perforatum*). Caution should be observed when these active substances are combined

with erlotinib. Alternate treatments lacking potent CYP3A4 inducing activity should be considered when possible.

International Normalized Ratio (INR) elevations, and bleeding events including gastrointestinal bleeding have been reported in clinical studies, some associated with concomitant warfarin administration (see section 4.8) and some with concomitant NSAID administration. Patients taking warfarin or other coumarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR.

Results of a pharmacokinetic interaction study indicated a significant 2.8-, 1.5- and 9-fold reduced AUC_{inf} , C_{max} and plasma concentration at 24 hours, respectively, after administration of Tarceva in smokers as compared to non-smokers (see section 5.2). Therefore, patients who are still smoking should be encouraged to stop smoking as early as possible before initiation of treatment with Tarceva, 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 (PPI), decreased the erlotinib exposure [AUC] and maximum concentration [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 H₂-receptor antagonist, decreased erlotinib exposure [AUC] and maximum concentrations [C_{max}] by 33% and 54%, respectively. 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 maximum concentrations [C_{max}] decreased only by 15% and 17%, respectively. The effect of antacids on the absorption of erlotinib have not been investigated but absorption may be impaired, leading to lower plasma levels. In summary, the combination of erlotinib with proton pump inhibitors should be avoided. If the use of antacids is considered necessary during treatment with Tarceva, they should be taken at least 4 hours before or 2 hours after the daily dose of Tarceva. If the use of ranitidine is considered, it should be used in a staggered manner; i.e. Tarceva must be taken at least 2 hours before or 10 hours after ranitidine dosing.

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 AUC_{0-48} 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 C_{max} 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.

4.6 Pregnancy and lactation

There are no studies in pregnant women using erlotinib. Studies in animals have shown some reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Women of

childbearing potential must be advised to avoid pregnancy while on Tarceva. Adequate contraceptive methods should be used during therapy, and for at least 2 weeks after completing therapy. Treatment should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the foetus.

It is not known whether erlotinib is excreted in human milk. Because of the potential harm to the infant, mothers should be advised against breastfeeding while receiving Tarceva.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Non-small cell lung cancer (Tarceva administered as monotherapy):

In a randomized double-blind study (BR.21; Tarceva administered as second line therapy), rash (75 %) and diarrhoea (54 %) were the most commonly reported adverse drug reactions (ADRs). Most were Grade 1/2 in severity and manageable without intervention. Grade 3/4 rash and diarrhoea occurred in 9 % and 6 %, respectively in Tarceva-treated patients and each resulted in study discontinuation in 1 % of patients. Dose reduction for rash and diarrhoea was needed in 6 % and 1 % of patients, respectively. In study BR.21, the median time to onset of rash was 8 days, and the median time to onset of diarrhoea was 12 days.

In general, rash manifests as a mild or moderate erythematous and papulopustular rash, which may occur or worsen in sun exposed areas. For patients who are exposed to sun, protective clothing, and/or use of sun screen (e.g. mineral-containing) may be advisable.

Adverse events occurring more frequently (≥ 3 %) in Tarceva-treated patients than in the placebo group in the pivotal study BR.21, and in at least 10 % of patients in the Tarceva group, are summarised by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Grade in Table 1.

Table 1: Very common ADRs in study BR.21

NCI-CTC Grade	Erlotinib N = 485			Placebo N = 242		
	Any Grade	3	4	Any Grade	3	4
MedDRA Preferred Term	%	%	%	%	%	%
Total patients with any AE	99	40	22	96	36	22
<i>Infections and infestations</i>						
Infection*	24	4	0	15	2	0
<i>Metabolism and nutrition disorders</i>						
Anorexia	52	8	1	38	5	<1
<i>Eye disorders</i>						
Conjunctivitis	12	<1	0	2	<1	0
Keratoconjunctivitis sicca	12	0	0	3	0	0
<i>Respiratory, thoracic and mediastinal disorders</i>						
Dyspnoea	41	17	11	35	15	11
Cough	33	4	0	29	2	0

NCI-CTC Grade	Erlotinib N = 485			Placebo N = 242		
	Any Grade	3	4	Any Grade	3	4
MedDRA Preferred Term	%	%	%	%	%	%
<i>Gastrointestinal disorders</i>						
Diarrhoea**	54	6	<1	18	<1	0
Nausea	33	3	0	24	2	0
Vomiting	23	2	<1	19	2	0
Stomatitis	17	<1	0	3	0	0
Abdominal pain	11	2	<1	7	1	<1
<i>Skin and subcutaneous tissue disorders</i>						
Rash***	75	8	<1	17	0	0
Pruritus	13	<1	0	5	0	0
Dry skin	12	0	0	4	0	0
<i>General disorders and administration site conditions</i>						
Fatigue	52	14	4	45	16	4

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

** Can lead to dehydration, hypokalemia and renal failure.

*** Rash included dermatitis acneiform.

In another double-blind, randomized, placebo-controlled Phase III study BO18192 (SATURN); Tarceva was administered as maintenance after first-line chemotherapy. SATURN was conducted in 889 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 Tarceva in study BO18192 were rash and diarrhoea (any Grade 49% and 20%, respectively), most were Grade 1/2 in severity and manageable without intervention. Grade 3 rash and diarrhoea occurred in 6% and 2% of patients, respectively. No Grade 4 rash or diarrhoea was observed. Rash and diarrhoea resulted in discontinuation of Tarceva in 1% and <1% of patients, respectively. Dose modifications (interruptions or reductions) for rash and diarrhoea were needed in 8.3% and 3% of patients, respectively.

Pancreatic cancer (Tarceva administered concurrently with gemcitabine):

The most common adverse reactions in pivotal 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 each reported in 5 % of patients. The median time to onset of rash and diarrhoea was 10 days and 15 days, respectively. Rash and diarrhoea each resulted in dose reductions in 2 % of patients, and resulted in study discontinuation in up to 1 % of patients receiving Tarceva plus gemcitabine.

Adverse events occurring more frequently (≥ 3 %) in Tarceva 100 mg plus gemcitabine-treated patients than in the placebo plus gemcitabine group in the pivotal study PA.3, and in at least 10 % of patients in the Tarceva 100 mg plus gemcitabine group, are summarised by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Grade in Table 2.

Table 2: Very common ADRs in study PA.3 (100 mg cohort)

NCI-CTC Grade	Erlotinib N = 259			Placebo N = 256		
	Any Grade	3	4	Any Grade	3	4
MedDRA Preferred Term	%	%	%	%	%	%
Total patients with any AE	99	48	22	97	48	16
<i>Infections and infestations</i>						
Infection*	31	3	<1	24	6	<1
<i>Metabolism and nutrition disorders</i>						
Weight decreased	39	2	0	29	<1	0
<i>Psychiatric disorders</i>						
Depression	19	2	0	14	<1	0
<i>Nervous system disorders</i>						
Headache	15	<1	0	10	0	0
Neuropathy	13	1	<1	10	<1	0
<i>Respiratory, thoracic and mediastinal disorders</i>						
Cough	16	0	0	11	0	0
<i>Gastrointestinal disorders</i>						
Diarrhoea**	48	5	<1	36	2	0
Stomatitis	22	<1	0	12	0	0
Dyspepsia	17	<1	0	13	<1	0
Flatulence	13	0	0	9	<1	0
<i>Skin and subcutaneous tissue disorders</i>						
Rash***	69	5	0	30	1	0
Alopecia	14	0	0	11	0	0
<i>General disorders and administration site conditions</i>						
Pyrexia	36	3	0	30	4	0
Fatigue	73	14	2	70	13	2
Rigors	12	0	0	9	0	0

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

** Can lead to dehydration, hypokalemia and renal failure.

*** Rash included dermatitis acneiform.

Other Observations:

Safety evaluation of 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 or 150 mg in combination with gemcitabine.

The following terms are used to rank the undesirable effects by frequency: very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1000); very rare (<1/10,000) including isolated reports.

The following adverse reactions have been observed in patients who received Tarceva administered as single agent and patients who received Tarceva concurrently with chemotherapy.

Very common ADR's are presented in Tables 1 and 2, ADR's in other frequency categories are summarized below.

Gastrointestinal disorders:

- Common:* Gastrointestinal bleeding. In clinical studies, some cases have been associated with concomitant warfarin administration (see section 4.5) and some with concomitant NSAID administration.
- Uncommon:* Gastrointestinal perforations.

Skin and subcutaneous tissue disorders:

- Common:* Alopecia.
- Common (in PA.3):* Dry skin.
- Common:* Paronychia.
- Uncommon:* Hirsutism, eyebrow changes and brittle and loose nails.
- Uncommon:* Mild skin reactions such as hyperpigmentation.
- Very rare:* Cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal.

Hepato-biliary disorders:

- Very common (in PA.3)*
- Common (in BR.21):* Liver function test abnormalities (including increased alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). These were mainly mild or moderate in severity, transient in nature or associated with liver metastases.
- Rare:* 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 4.4).

Eye disorders:

- Common:* Keratitis.
- Common:* Conjunctivitis in study PA.3.
- Uncommon:* Eyelash changes (including in-growing eyelashes, excessive growth and thickening of the eyelashes).
- Very rare:* Corneal ulcerations and perforations.

Respiratory, thoracic and mediastinal disorders:

- Common:* Epistaxis.
- Uncommon:* Serious interstitial lung disease (ILD), including fatalities, in patients receiving Tarceva for treatment of NSCLC or other advanced solid tumours (see section 4.4).

4.9 Overdose

Single oral doses of Tarceva up to 1000 mg erlotinib 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 diarrhoea, rash and possibly increased activity of liver aminotransferases may occur above the recommended dose. In case of suspected overdose, Tarceva should be withheld and symptomatic treatment initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agent, ATC code: L01XE03

Erlotinib is an epidermal growth factor receptor/human epidermal growth factor receptor type 1 (EGFR also known as HER1) tyrosine kinase inhibitor. Erlotinib potently inhibits the intracellular phosphorylation of EGFR. EGFR is expressed on the cell surface of normal cells and cancer cells. In non-clinical models, inhibition of EGFR phosphotyrosine results in cell stasis and/or death.

Non-small cell lung cancer (Tarceva administered as monotherapy):

Maintenance after first-line chemotherapy:

The efficacy and safety of Tarceva as maintenance after first-line chemotherapy for NSCLC was demonstrated 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 after 4 cycles of platinum-based doublet chemotherapy. Patients were randomized 1:1 to receive Tarceva 150 mg or placebo orally once daily until disease progression. The primary endpoint of the study was progression free survival (PFS) in all patients and in patients with an EGFR IHC positive tumour. Baseline demographic and disease characteristics were well balanced between the two treatment arms. Patients with ECOG PS>1, significant hepatic or renal co-morbidities were not included in the study.

- ITT population results:

The primary PFS analysis in all patients (n=889) showed a PFS hazard ratio (HR) of 0.71 (95 % CI, 0.62 to 0.82; p<0.0001) for the Tarceva group relative to the placebo group. The mean PFS was 22.4 weeks in the Tarceva group compared with 16.0 weeks in the placebo group. PFS results were confirmed by an independent review of the scans. Quality of life data did not suggest a detrimental effect from erlotinib compared with placebo.

A PFS HR of 0.69 (95% CI, 0.58 to 0.82; p < 0.0001) was observed in the coprimary patient population with EGFR IHC positive tumours (n=621). The mean PFS was 22.8 weeks in the Tarceva group (range 0.1 to 78.9 weeks) compared with 16.2 weeks in the placebo group (range 0.1 to 88.1 weeks). The progression free survival rate at 6 months was 27% and 16%, respectively for Tarceva and placebo.

Concerning the secondary endpoint of overall survival, the HR was 0.81 (95% CI, 0.70 to 0.95; p=0.0088). The median overall survival was 12.0 months in the Tarceva group versus 11.0 months in the placebo group.

Patients with EGFR activating mutations had the largest benefit (n= 49, PFS HR=0.10, 95 % CI, 0.04 to 0.25; p<0.0001). In patients with EGFR wild type tumours (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).

- Patients with Stable Disease after chemotherapy:

Patients with stable disease (SD) (n= 487) had a PFS HR of 0.68 (95% CI, 0.56 to 0.83; p<0.0001; median 12.1 weeks in the Tarceva group and 11.3 weeks in the placebo group) and an overall survival HR of 0.72 (95% CI, 0.59 to 0.89; p= 0.0019; median 11.9 months in the Tarceva group and 9.6 months in the placebo group).

The effect on overall survival was explored across different subsets of patients with SD receiving Tarceva. This did not show major qualitative differences between patients with squamous cell carcinoma (HR 0.67, 95% CI, 0.48-0.92) and non-squamous cell carcinoma (HR 0.76, 95% CI 0.59-1.00) and between patients with EGFR activating mutations (HR 0.48, 95% 0.14-1.62) and without EGFR activating mutations (HR 0.65, 95% CI 0.48-0.87).

Treatment after failure of at least one prior chemotherapy regimen:

The efficacy and safety of Tarceva as second-/ third-line therapy was demonstrated in a randomised, double-blind, placebo-controlled trial (BR.21), in 731 patients with locally advanced or metastatic NSCLC after failure of at least one chemotherapy regimen. Patients were randomised 2:1 to receive Tarceva 150 mg or placebo orally once daily. Study endpoints included overall survival,

progression-free survival (PFS), response rate, duration of response, time to deterioration of lung cancer-related symptoms (cough, dyspnoea and pain), and safety. The primary endpoint was survival.

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

The adjusted hazard ratio (HR) 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 percent of patients alive at 12 months was 31.2 % and 21.5 %, for the Tarceva and placebo groups, respectively. The median overall survival was 6.7 months in the Tarceva group (95 % CI, 5.5 to 7.8 months) compared with 4.7 months in the placebo group (95 % CI, 4.1 to 6.3 months).

The effect on overall survival was explored across different patient subsets. The effect of Tarceva 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, 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, 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, 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).

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

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

The objective response rate by RECIST in the Tarceva group was 8.9 % (95 % CI, 6.4 to 12.0).

The first 330 patients were centrally assessed (response rate 6.2 %); 401 patients were investigator-assessed (response rate 11.2 %).

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

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 0.82 (95 % CI, 0.68 to 0.99) among patients whose best response was stable disease or progressive disease.

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

Pancreatic cancer (Tarceva administered concurrently with gemcitabine in study PA.3):

The efficacy and safety of Tarceva in combination with gemcitabine as a first-line treatment was assessed in a randomised, double-blind, placebo-controlled trial in patients with locally advanced, unresectable or metastatic pancreatic cancer. Patients were randomised to receive Tarceva or placebo once daily on a continuous schedule plus gemcitabine IV (1000 mg/m², Cycle 1 - Days 1, 8, 15, 22, 29, 36 and 43 of an 8 week cycle; Cycle 2 and subsequent cycles - Days 1, 8 and 15 of a 4 week cycle

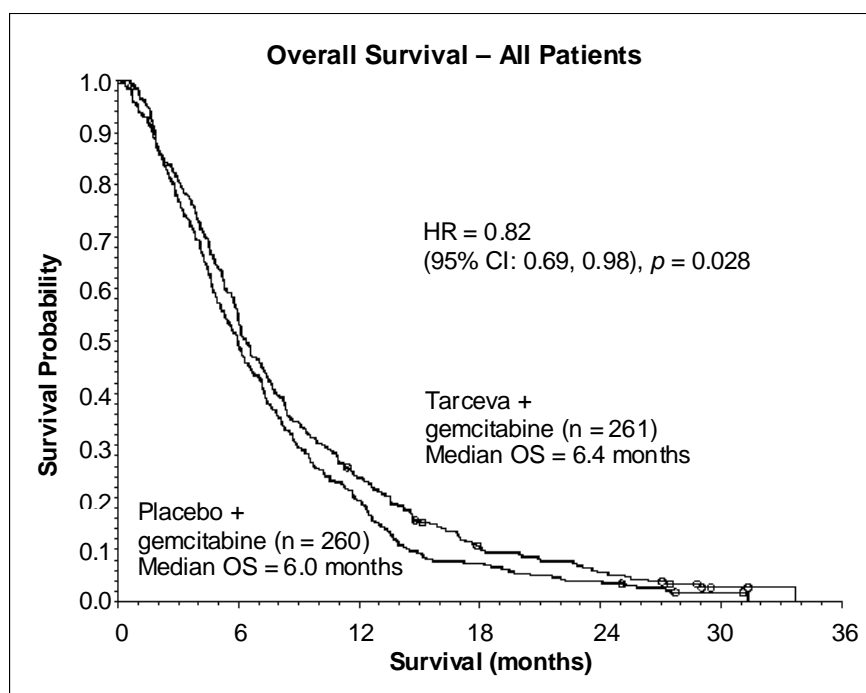
[approved dose and schedule for pancreatic cancer, see the gemcitabine SPC]). Tarceva or placebo was taken orally once daily until disease progression or unacceptable toxicity. The primary endpoint was overall survival.

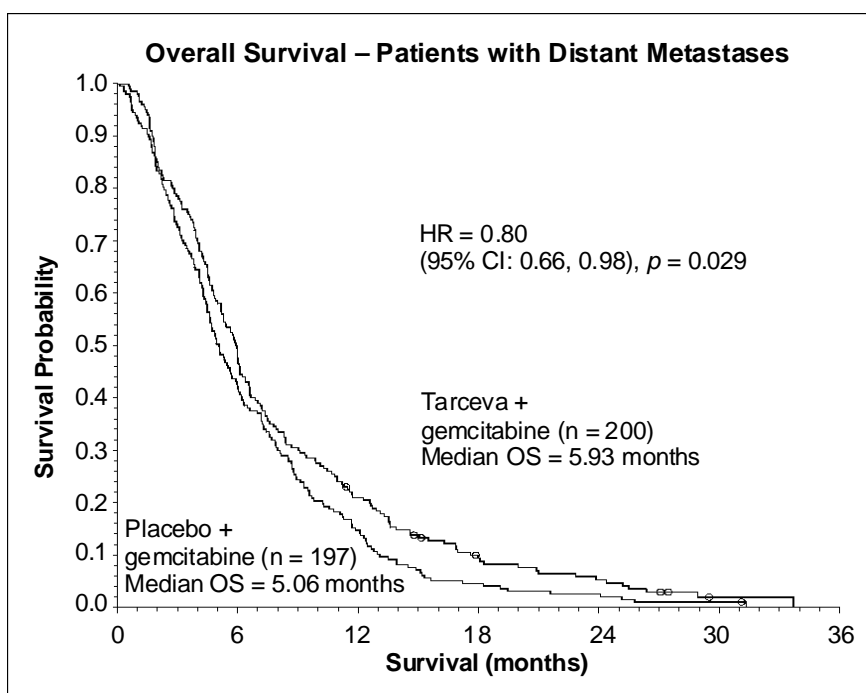
Baseline demographic and disease characteristics of the patients were similar between the 2 treatment groups, 100 mg Tarceva plus gemcitabine or placebo plus gemcitabine, except for a slightly larger proportion of females in the erlotinib/gemcitabine arm compared with the placebo/gemcitabine arm:

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

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

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





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

In a post-hoc analysis, patients on Tarceva who developed a rash had a longer overall survival compared to patients who did not develop rash (median OS 7.2 months vs 5 months, HR:0.61). 90% of patients on Tarceva developed rash within the first 44 days. The median time to onset of rash was 10 days.

5.2 Pharmacokinetic properties

Absorption: After oral administration, erlotinib peak plasma levels are obtained in approximately 4 hours after oral dosing. A study in normal healthy volunteers provided an estimate of the absolute bioavailability of 59 %. The exposure after an oral dose may be increased by food.

Distribution: Erlotinib has a mean apparent volume of distribution of 232 l and distributes into tumour tissue of humans. In a study of 4 patients (3 with non-small cell lung cancer [NSCLC], and 1 with laryngeal cancer) receiving 150 mg daily oral doses of Tarceva, tumour samples from surgical excisions on Day 9 of treatment revealed tumour concentrations of erlotinib that averaged 1,185 ng/g of tissue. This corresponded to an overall average of 63 % (range 5-161 %) of the steady state observed peak plasma concentrations. The primary active metabolites were present in tumour at concentrations averaging 160 ng/g tissue, which corresponded to an overall average of 113 % (range 88-130 %) of the observed steady state peak plasma concentrations. Plasma protein binding is approximately 95 %. Erlotinib binds to serum albumin and alpha-1 acid glycoprotein (AAG).

Metabolism: Erlotinib is metabolised in the liver by the hepatic cytochromes in humans, primarily CYP3A4 and to a lesser extent by CYP1A2. Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung, and 1B1 in tumour tissue potentially contribute to the metabolic clearance of erlotinib.

There are three main metabolic pathways identified: 1) O-demethylation of either side chain or both, followed by oxidation to the carboxylic acids; 2) oxidation of the acetylene moiety followed by hydrolysis to the aryl carboxylic acid; and 3) aromatic hydroxylation of the phenyl-acetylene moiety. The primary metabolites OSI-420 and OSI-413 of erlotinib produced by O-demethylation of either side chain have comparable potency to erlotinib in non-clinical *in vitro* assays and *in vivo* tumour

models. They are present in plasma at levels that are <10 % of erlotinib and display similar pharmacokinetics as erlotinib.

Elimination: Erlotinib is excreted predominantly as metabolites via the faeces (>90 %) with renal elimination accounting for only a small amount (approximately 9 %) of an oral dose. Less than 2 % of the orally administered dose is excreted as parent substance. A population pharmacokinetic analysis in 591 patients receiving single agent Tarceva shows a mean apparent clearance of 4.47 l/hour with a median half-life of 36.2 hours. Therefore, the time to reach steady state plasma concentration would be expected to occur in approximately 7-8 days.

Pharmacokinetics in special populations:

Based on population pharmacokinetic analysis, no clinically significant relationship between predicted apparent clearance and patient age, bodyweight, gender and ethnicity were observed. Patient factors, which correlated with erlotinib pharmacokinetics, were serum total bilirubin, AAG and current smoking. Increased serum concentrations of total bilirubin and AAG concentrations were associated with a reduced erlotinib clearance. The clinical relevance of these differences is unclear. However, smokers had an increased rate of erlotinib clearance. This was confirmed in a pharmacokinetic study in non-smoking and currently cigarette smoking healthy subjects receiving a single oral dose of 150 mg erlotinib. The geometric mean of the C_{max} was 1056 ng/mL in the non-smokers and 689 ng/mL in the smokers with a mean ratio for smokers to non-smokers of 65.2 % (95 % CI: 44.3 to 95.9, $p = 0.031$). The geometric mean of the AUC_{0-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 C_{24h} 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 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 ($n=17$).

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, the presence of an opioid appeared to increase exposure by about 11 %.

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 covariants 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.

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

Hepatic impairment: Erlotinib is primarily cleared by the liver. In patients with solid tumours and with moderately impaired hepatic function (Child-Pugh score 7-9), geometric mean erlotinib AUC_{0-t} and C_{max} was 27000 ng•h/mL and 805 ng/mL, respectively, as compared to 29300 ng•h/mL and 1090 ng/mL in patients with adequate hepatic function including patients with primary liver cancer or hepatic metastases. Although the C_{max} was statistically significant lower in moderately hepatic impaired patients, this difference is not considered clinically relevant. No data are available regarding the influence of severe hepatic dysfunction on the pharmacokinetics of erlotinib. In population

pharmacokinetic analysis, increased serum concentrations of total bilirubin were associated with a slower rate of erlotinib clearance.

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

5.3 Preclinical safety data

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

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

Erlotinib tested negative in conventional genotoxicity studies. Carcinogenicity studies have not been performed.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate
Cellulose, microcrystalline (E460)
Sodium starch glycolate Type A
Sodium laurilsulfate
Magnesium stearate (E470 b)

Tablet coat:

Hydroxypropyl cellulose (E463)
Titanium dioxide (E171)
Macrogol
Hypromellose (E464)

Printing ink grey:

Shellac (E904)
Iron oxide yellow (E172)
Iron oxide black (E172)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC blister sealed with aluminium foil containing 30 tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/311/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 September 2005

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Tarceva 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tarceva 150 mg

One film-coated tablet contains 150 mg erlotinib (as erlotinib hydrochloride).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White to yellowish, round, biconvex tablets with 'Tarceva 150' and logo printed in brown on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-small cell lung cancer (NSCLC):

Tarceva is indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after 4 cycles of standard platinum-based first-line chemotherapy.

Tarceva is also 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 (see section 5.1).

Pancreatic cancer:

Tarceva in combination with gemcitabine is indicated for the treatment of patients with metastatic pancreatic cancer.

When prescribing Tarceva, factors associated with prolonged survival should be taken into account (see section 4.2 and 5.1).

No survival advantage could be shown for patients with locally advanced disease.

4.2 Posology and method of administration

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

Non-small cell lung cancer:

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 5.1).

When dose adjustment is necessary, reduce in 50 mg steps (see section 4.4).

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

Concomitant use of CYP3A4 substrates and modulators may require dose adjustment (see section 4.5).

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 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 (see section 5.2).

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 5.2). 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. Efficacy and long term safety of a dose higher than the recommended starting doses have not been established in patients who continue to smoke cigarettes (see sections 4.5 and 5.2). Therefore, current smokers should be advised to stop smoking, as plasma concentrations of erlotinib in smokers as compared to non-smokers are reduced.

4.3 Contraindications

Severe hypersensitivity to erlotinib or to any of the excipients.

4.4 Special warnings and precautions for use

Potent inducers of CYP3A4 may reduce the efficacy of erlotinib whereas potent inhibitors of CYP3A4 may lead to increased toxicity. Concomitant treatment with these types of agents should be avoided (see section 4.5).

Current smokers should be advised to stop smoking, as plasma concentrations of erlotinib in smokers as compared to non-smokers are reduced. The degree of reduction is likely to be clinically significant (see section 4.5).

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 ILD (0.8 %) was the same in both the placebo and Tarceva groups. 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. The overall incidence in Tarceva-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) is approximately 0.6 % compared to 0.2 % in patients on placebo. Reported diagnoses in patients suspected of having ILD-like events included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome (ARDS), alveolitis, and lung infiltration. Symptoms started from a few days to several months after initiating Tarceva therapy. Confounding or contributing factors such as concomitant or prior chemotherapy,

prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections were frequent.

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 4.8).

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 4.8). 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), 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.

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 4.8). Tarceva is not recommended for use in patients with severe hepatic dysfunction.

Patients receiving Tarceva are at increased risk of developing gastrointestinal perforation, which was observed uncommonly. 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 4.8).

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 4.8). Tarceva treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions.

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 4.8).

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.

Erlotinib is characterised by a decrease in solubility at pH above 5. Drugs that alter the pH of the upper GI tract, like proton pump inhibitors, H₂ antagonists and antacids, may alter the solubility of erlotinib and hence its bioavailability. Increasing the dose of Tarceva when coadministered with such agents is not likely to compensate for the loss of exposure. Combination of erlotinib with proton pump inhibitors should be avoided. The effects of concomitant administration of erlotinib with H₂ antagonists and antacids are unknown; however, reduced bioavailability is likely. Therefore, concomitant administration of these combinations should be avoided (see section 4.5). If the use of

antacids is considered necessary during treatment with Tarceva, they should be taken at least 4 hours before or 2 hours after the daily dose of Tarceva.

4.5 Interaction 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.

When erlotinib was co-administered with ciprofloxacin, a moderate CYP1A2 inhibitor, the erlotinib exposure [AUC] increased significantly by 39 %, while no statistically significant change in C_{max} was found. Similarly, the exposure to the active metabolite increased by about 60% and 48% for AUC and C_{max} , respectively. The clinical relevance of this increase has not been established. Caution should be exercised when ciprofloxacin or potent CYP1A2 inhibitors (e.g. fluvoxamine) are combined with erlotinib. If adverse events related to erlotinib are observed, the dose of erlotinib may be reduced.

Pretreatment or coadministration of Tarceva did not alter the clearance of the prototypical CYP3A4 substrates, midazolam and erythromycin, but did appear to decrease the oral bioavailability of midazolam by up to 24%. In another clinical study, erlotinib was shown not to affect pharmacokinetics of the concomitantly administered CYP3A4/2C8 substrate paclitaxel. Significant interactions with the clearance of other CYP3A4 substrates are therefore unlikely.

The inhibition of glucuronidation may cause interactions with medicinal products which are substrates of UGT1A1 and exclusively cleared by this pathway. Patients with low expression levels of UGT1A1 or genetic glucuronidation disorders (e.g. Gilbert's disease) may exhibit increased serum concentrations of bilirubin and must be treated with caution.

Erlotinib is metabolised in the liver by the hepatic cytochromes in humans, primarily CYP3A4 and to a lesser extent by CYP1A2. Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung, and CYP1B1 in tumour tissue also potentially contribute to the metabolic clearance of erlotinib. Potential interactions may occur with active substances which are metabolised by, or are inhibitors or inducers of, these enzymes.

Potent inhibitors of CYP3A4 activity decrease erlotinib metabolism and increase erlotinib plasma concentrations. 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 % of AUC and 69 % of C_{max}). Therefore, caution should be used when erlotinib is combined with a potent CYP3A4 inhibitor, e.g. azole antifungals (i.e. ketoconazole, itraconazole, voriconazole), protease inhibitors, erythromycin or clarithromycin. If necessary the dose of erlotinib should be reduced, particularly if toxicity is observed.

Potent inducers of CYP3A4 activity increase erlotinib metabolism and significantly decrease erlotinib plasma concentrations. In a clinical study, the concomitant use of erlotinib and rifampicin (600 mg orally once daily for 7 days), a potent CYP3A4 inducer, resulted in a 69 % decrease in the median erlotinib AUC. 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. Co-administration of Tarceva with CYP3A4 inducers should therefore be avoided. 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 (including renal and liver functions and serum electrolytes) is closely monitored, and if well tolerated for more than 2 weeks, further increase to 450 mg could be considered with close safety monitoring. Reduced exposure may also occur with other inducers e.g. phenytoin, carbamazepine, barbiturates or St. Johns Wort (*hypericum perforatum*). Caution should be observed when these active substances are combined

with erlotinib. Alternate treatments lacking potent CYP3A4 inducing activity should be considered when possible.

International Normalized Ratio (INR) elevations, and bleeding events including gastrointestinal bleeding have been reported in clinical studies, some associated with concomitant warfarin administration (see section 4.8) and some with concomitant NSAID administration. Patients taking warfarin or other coumarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR.

Results of a pharmacokinetic interaction study indicated a significant 2.8-, 1.5- and 9-fold reduced AUC_{inf} , C_{max} and plasma concentration at 24 hours, respectively, after administration of Tarceva in smokers as compared to non-smokers (see section 5.2). Therefore, patients who are still smoking should be encouraged to stop smoking as early as possible before initiation of treatment with Tarceva, 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 (PPI), decreased the erlotinib exposure [AUC] and maximum concentration [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 H₂-receptor antagonist, decreased erlotinib exposure [AUC] and maximum concentrations [C_{max}] by 33% and 54%, respectively. 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 maximum concentrations [C_{max}] decreased only by 15% and 17% , respectively. The effect of antacids on the absorption of erlotinib have not been investigated but absorption may be impaired, leading to lower plasma levels. In summary, the combination of erlotinib with proton pump inhibitors should be avoided. If the use of antacids is considered necessary during treatment with Tarceva, they should be taken at least 4 hours before or 2 hours after the daily dose of Tarceva. If the use of ranitidine is considered, it should be used in a staggered manner; i.e. Tarceva must be taken at least 2 hours before or 10 hours after ranitidine dosing.

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 AUC_{0-48} 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 C_{max} 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.

4.6 Pregnancy and lactation

There are no studies in pregnant women using erlotinib. Studies in animals have shown some reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Women of

childbearing potential must be advised to avoid pregnancy while on Tarceva. Adequate contraceptive methods should be used during therapy, and for at least 2 weeks after completing therapy. Treatment should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the foetus.

It is not known whether erlotinib is excreted in human milk. Because of the potential harm to the infant, mothers should be advised against breastfeeding while receiving Tarceva.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Non-small cell lung cancer (Tarceva administered as monotherapy):

In a randomized double-blind study (BR.21; Tarceva administered as second line therapy), rash (75 %) and diarrhoea (54 %) were the most commonly reported adverse drug reactions (ADRs). Most were Grade 1/2 in severity and manageable without intervention. Grade 3/4 rash and diarrhoea occurred in 9 % and 6 %, respectively in Tarceva-treated patients and each resulted in study discontinuation in 1 % of patients. Dose reduction for rash and diarrhoea was needed in 6 % and 1 % of patients, respectively. In study BR.21, the median time to onset of rash was 8 days, and the median time to onset of diarrhoea was 12 days.

In general, rash manifests as a mild or moderate erythematous and papulopustular rash, which may occur or worsen in sun exposed areas. For patients who are exposed to sun, protective clothing, and/or use of sun screen (e.g. mineral-containing) may be advisable.

Adverse events occurring more frequently (≥ 3 %) in Tarceva-treated patients than in the placebo group in the pivotal study BR.21, and in at least 10 % of patients in the Tarceva group, are summarised by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Grade in Table 1.

Table 1: Very common ADRs in study BR.21

NCI-CTC Grade	Erlotinib N = 485			Placebo N = 242		
	Any Grade	3	4	Any Grade	3	4
MedDRA Preferred Term	%	%	%	%	%	%
Total patients with any AE	99	40	22	96	36	22
<i>Infections and infestations</i>						
Infection*	24	4	0	15	2	0
<i>Metabolism and nutrition disorders</i>						
Anorexia	52	8	1	38	5	<1
<i>Eye disorders</i>						
Conjunctivitis	12	<1	0	2	<1	0
Keratoconjunctivitis sicca	12	0	0	3	0	0
<i>Respiratory, thoracic and mediastinal disorders</i>						
Dyspnoea	41	17	11	35	15	11
Cough	33	4	0	29	2	0

NCI-CTC Grade	Erlotinib N = 485			Placebo N = 242		
	Any Grade	3	4	Any Grade	3	4
MedDRA Preferred Term	%	%	%	%	%	%
<i>Gastrointestinal disorders</i>						
Diarrhoea**	54	6	<1	18	<1	0
Nausea	33	3	0	24	2	0
Vomiting	23	2	<1	19	2	0
Stomatitis	17	<1	0	3	0	0
Abdominal pain	11	2	<1	7	1	<1
<i>Skin and subcutaneous tissue disorders</i>						
Rash***	75	8	<1	17	0	0
Pruritus	13	<1	0	5	0	0
Dry skin	12	0	0	4	0	0
<i>General disorders and administration site conditions</i>						
Fatigue	52	14	4	45	16	4

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

** Can lead to dehydration, hypokalemia and renal failure.

*** Rash included dermatitis acneiform.

In another double-blind, randomized, placebo-controlled Phase III study BO18192 (SATURN); Tarceva was administered as maintenance after first-line chemotherapy. SATURN was conducted in 889 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 Tarceva in study BO18192 were rash and diarrhoea (any Grade 49% and 20%, respectively), most were Grade 1/2 in severity and manageable without intervention. Grade 3 rash and diarrhoea occurred in 6% and 2% of patients, respectively. No Grade 4 rash or diarrhoea was observed. Rash and diarrhoea resulted in discontinuation of Tarceva in 1% and <1% of patients, respectively. Dose modifications (interruptions or reductions) for rash and diarrhoea were needed in 8.3% and 3% of patients, respectively.

Pancreatic cancer (Tarceva administered concurrently with gemcitabine):

The most common adverse reactions in pivotal 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 each reported in 5 % of patients. The median time to onset of rash and diarrhoea was 10 days and 15 days, respectively. Rash and diarrhoea each resulted in dose reductions in 2 % of patients, and resulted in study discontinuation in up to 1 % of patients receiving Tarceva plus gemcitabine.

Adverse events occurring more frequently (≥ 3 %) in Tarceva 100 mg plus gemcitabine-treated patients than in the placebo plus gemcitabine group in the pivotal study PA.3, and in at least 10 % of patients in the Tarceva 100 mg plus gemcitabine group, are summarised by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Grade in Table 2.

Table 2: Very common ADRs in study PA.3 (100 mg cohort)

NCI-CTC Grade	Erlotinib N = 259			Placebo N = 256		
	Any Grade	3	4	Any Grade	3	4
MedDRA Preferred Term	%	%	%	%	%	%
Total patients with any AE	99	48	22	97	48	16
<i>Infections and infestations</i>						
Infection*	31	3	<1	24	6	<1
<i>Metabolism and nutrition disorders</i>						
Weight decreased	39	2	0	29	<1	0
<i>Psychiatric disorders</i>						
Depression	19	2	0	14	<1	0
<i>Nervous system disorders</i>						
Headache	15	<1	0	10	0	0
Neuropathy	13	1	<1	10	<1	0
<i>Respiratory, thoracic and mediastinal disorders</i>						
Cough	16	0	0	11	0	0
<i>Gastrointestinal disorders</i>						
Diarrhoea**	48	5	<1	36	2	0
Stomatitis	22	<1	0	12	0	0
Dyspepsia	17	<1	0	13	<1	0
Flatulence	13	0	0	9	<1	0
<i>Skin and subcutaneous tissue disorders</i>						
Rash***	69	5	0	30	1	0
Alopecia	14	0	0	11	0	0
<i>General disorders and administration site conditions</i>						
Pyrexia	36	3	0	30	4	0
Fatigue	73	14	2	70	13	2
Rigors	12	0	0	9	0	0

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

** Can lead to dehydration, hypokalemia and renal failure.

*** Rash included dermatitis acneiform.

Other Observations:

Safety evaluation of 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 or 150 mg in combination with gemcitabine.

The following terms are used to rank the undesirable effects by frequency: very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1000); very rare (<1/10,000) including isolated reports.

The following adverse reactions have been observed in patients who received Tarceva administered as single agent and patients who received Tarceva concurrently with chemotherapy.

Very common ADR's are presented in Tables 1 and 2, ADR's in other frequency categories are summarized below.

Gastrointestinal disorders:

- Common:* Gastrointestinal bleeding. In clinical studies, some cases have been associated with concomitant warfarin administration (see section 4.5) and some with concomitant NSAID administration.
- Uncommon:* Gastrointestinal perforations.

Skin and subcutaneous tissue disorders:

- Common:* Alopecia.
- Common (in PA.3):* Dry skin.
- Common:* Paronychia.
- Uncommon:* Hirsutism, eyebrow changes and brittle and loose nails.
- Uncommon:* Mild skin reactions such as hyperpigmentation.
- Very rare:* Cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal.

Hepato-biliary disorders:

- Very common (in PA.3)*
- Common (in BR.21):* Liver function test abnormalities (including increased alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). These were mainly mild or moderate in severity, transient in nature or associated with liver metastases.
- Rare:* 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 4.4).

Eye disorders:

- Common:* Keratitis.
- Common:* Conjunctivitis in study PA.3.
- Uncommon:* Eyelash changes (including in-growing eyelashes, excessive growth and thickening of the eyelashes).
- Very rare:* Corneal ulcerations and perforations.

Respiratory, thoracic and mediastinal disorders:

- Common:* Epistaxis.
- Uncommon:* Serious interstitial lung disease (ILD), including fatalities, in patients receiving Tarceva for treatment of NSCLC or other advanced solid tumours (see section 4.4).

4.9 Overdose

Single oral doses of Tarceva up to 1000 mg erlotinib 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 diarrhoea, rash and possibly increased activity of liver aminotransferases may occur above the recommended dose. In case of suspected overdose, Tarceva should be withheld and symptomatic treatment initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agent, ATC code: L01XE03

Erlotinib is an epidermal growth factor receptor/human epidermal growth factor receptor type 1 (EGFR also known as HER1) tyrosine kinase inhibitor. Erlotinib potently inhibits the intracellular phosphorylation of EGFR. EGFR is expressed on the cell surface of normal cells and cancer cells. In non-clinical models, inhibition of EGFR phosphotyrosine results in cell stasis and/or death.

Non-small cell lung cancer (Tarceva administered as monotherapy):

Maintenance after first-line chemotherapy:

The efficacy and safety of Tarceva as maintenance after first-line chemotherapy for NSCLC was demonstrated 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 after 4 cycles of platinum-based doublet chemotherapy. Patients were randomized 1:1 to receive Tarceva 150 mg or placebo orally once daily until disease progression. The primary endpoint of the study was progression free survival (PFS) in all patients and in patients with an EGFR IHC positive tumour. Baseline demographic and disease characteristics were well balanced between the two treatment arms. Patients with ECOG PS>1, significant hepatic or renal co-morbidities were not included in the study.

- ITT population results:

The primary PFS analysis in all patients (n=889) showed a PFS hazard ratio (HR) of 0.71 (95 % CI, 0.62 to 0.82; p<0.0001) for the Tarceva group relative to the placebo group. The mean PFS was 22.4 weeks in the Tarceva group compared with 16.0 weeks in the placebo group. PFS results were confirmed by an independent review of the scans. Quality of life data did not suggest a detrimental effect from erlotinib compared with placebo.

A PFS HR of 0.69 (95% CI, 0.58 to 0.82; p < 0.0001) was observed in the coprimary patient population with EGFR IHC positive tumours (n=621). The mean PFS was 22.8 weeks in the Tarceva group (range 0.1 to 78.9 weeks) compared with 16.2 weeks in the placebo group (range 0.1 to 88.1 weeks). The progression free survival rate at 6 months was 27% and 16%, respectively for Tarceva and placebo.

Concerning the secondary endpoint of overall survival, the HR was 0.81 (95% CI, 0.70 to 0.95; p=0.0088). The median overall survival was 12.0 months in the Tarceva group versus 11.0 months in the placebo group.

Patients with EGFR activating mutations had the largest benefit (n= 49, PFS HR=0.10, 95 % CI, 0.04 to 0.25; p<0.0001). In patients with EGFR wild type tumours (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).

- Patients with Stable Disease after chemotherapy:

Patients with stable disease (SD) (n= 487) had a PFS HR of 0.68 (95% CI, 0.56 to 0.83; p<0.0001; median 12.1 weeks in the Tarceva group and 11.3 weeks in the placebo group) and an overall survival HR of 0.72 (95% CI, 0.59 to 0.89; p= 0.0019; median 11.9 months in the Tarceva group and 9.6 months in the placebo group).

The effect on overall survival was explored across different subsets of patients with SD receiving Tarceva. This did not show major qualitative differences between patients with squamous cell carcinoma (HR 0.67, 95% CI, 0.48-0.92) and non-squamous cell carcinoma (HR 0.76, 95% CI 0.59-1.00) and between patients with EGFR activating mutations (HR 0.48, 95% CI 0.14-1.62) and without EGFR activating mutations (HR 0.65, 95% CI 0.48-0.87).

Treatment after failure of at least one prior chemotherapy regimen:

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

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

The adjusted hazard ratio (HR) 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 percent of patients alive at 12 months was 31.2 % and 21.5 %, for the Tarceva and placebo groups, respectively. The median overall survival was 6.7 months in the Tarceva group (95 % CI, 5.5 to 7.8 months) compared with 4.7 months in the placebo group (95 % CI, 4.1 to 6.3 months).

The effect on overall survival was explored across different patient subsets. The effect of Tarceva 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, 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, 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, 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).

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

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

The objective response rate by RECIST in the Tarceva group was 8.9 % (95 % CI, 6.4 to 12.0).

The first 330 patients were centrally assessed (response rate 6.2 %); 401 patients were investigator-assessed (response rate 11.2 %).

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

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 0.82 (95 % CI, 0.68 to 0.99) among patients whose best response was stable disease or progressive disease.

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

Pancreatic cancer (Tarceva administered concurrently with gemcitabine in study PA.3):

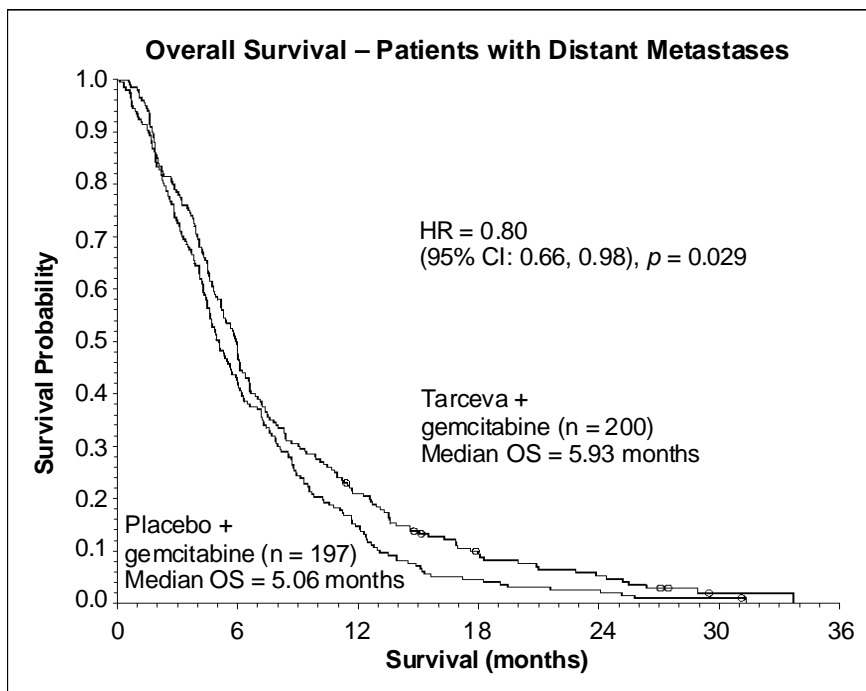
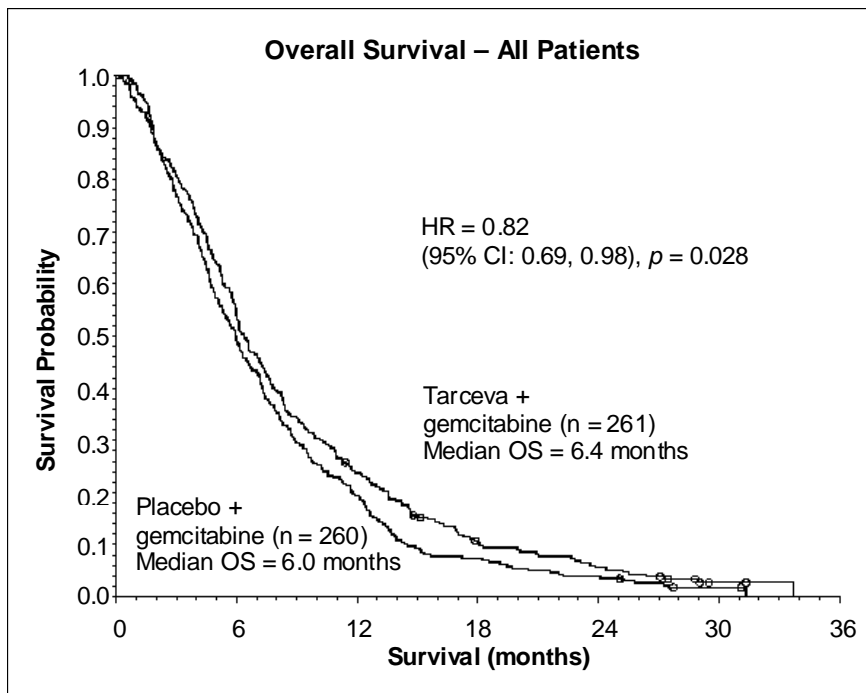
The efficacy and safety of Tarceva in combination with gemcitabine as a first-line treatment was assessed in a randomised, double-blind, placebo-controlled trial in patients with locally advanced, unresectable or metastatic pancreatic cancer. Patients were randomised to receive Tarceva or placebo once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

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

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

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

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



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

In a post-hoc analysis, patients on Tarceva who developed a rash had a longer overall survival compared to patients who did not develop rash (median OS 7.2 months vs 5 months, HR:0.61). 90% of patients on Tarceva developed rash within the first 44 days. The median time to onset of rash was 10 days.

5.2 Pharmacokinetic properties

Absorption: After oral administration, erlotinib peak plasma levels are obtained in approximately 4 hours after oral dosing. A study in normal healthy volunteers provided an estimate of the absolute bioavailability of 59%. The exposure after an oral dose may be increased by food.

Distribution: Erlotinib has a mean apparent volume of distribution of 232 l and distributes into tumour tissue of humans. In a study of 4 patients (3 with non-small cell lung cancer [NSCLC], and 1 with laryngeal cancer) receiving 150 mg daily oral doses of Tarceva, tumour samples from surgical excisions on Day 9 of treatment revealed tumour concentrations of erlotinib that averaged 1,185 ng/g of tissue. This corresponded to an overall average of 63 % (range 5-161 %) of the steady state observed peak plasma concentrations. The primary active metabolites were present in tumour at concentrations averaging 160 ng/g tissue, which corresponded to an overall average of 113 % (range 88-130 %) of the observed steady state peak plasma concentrations. Plasma protein binding is approximately 95 %. Erlotinib binds to serum albumin and alpha-1 acid glycoprotein (AAG).

Metabolism: Erlotinib is metabolised in the liver by the hepatic cytochromes in humans, primarily CYP3A4 and to a lesser extent by CYP1A2. Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung, and 1B1 in tumour tissue potentially contribute to the metabolic clearance of erlotinib.

There are three main metabolic pathways identified: 1) O-demethylation of either side chain or both, followed by oxidation to the carboxylic acids; 2) oxidation of the acetylene moiety followed by hydrolysis to the aryl carboxylic acid; and 3) aromatic hydroxylation of the phenyl-acetylene moiety. The primary metabolites OSI-420 and OSI-413 of erlotinib produced by O-demethylation of either side chain have comparable potency to erlotinib in non-clinical *in vitro* assays and *in vivo* tumour models. They are present in plasma at levels that are <10 % of erlotinib and display similar pharmacokinetics as erlotinib.

Elimination: Erlotinib is excreted predominantly as metabolites via the faeces (>90 %) with renal elimination accounting for only a small amount (approximately 9 %) of an oral dose. Less than 2 % of the orally administered dose is excreted as parent substance. A population pharmacokinetic analysis in 591 patients receiving single agent Tarceva shows a mean apparent clearance of 4.47 l/hour with a median half-life of 36.2 hours. Therefore, the time to reach steady state plasma concentration would be expected to occur in approximately 7-8 days.

Pharmacokinetics in special populations:

Based on population pharmacokinetic analysis, no clinically significant relationship between predicted apparent clearance and patient age, bodyweight, gender and ethnicity were observed. Patient factors, which correlated with erlotinib pharmacokinetics, were serum total bilirubin, AAG and current smoking. Increased serum concentrations of total bilirubin and AAG concentrations were associated with a reduced erlotinib clearance. The clinical relevance of these differences is unclear. However, smokers had an increased rate of erlotinib clearance. This was confirmed in a pharmacokinetic study in non-smoking and currently cigarette smoking healthy subjects receiving a single oral dose of 150 mg erlotinib. The geometric mean of the C_{max} was 1056 ng/mL in the non-smokers and 689 ng/mL in the smokers with a mean ratio for smokers to non-smokers of 65.2 % (95 % CI: 44.3 to 95.9, $p = 0.031$). The geometric mean of the AUC_{0-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 C_{24h} 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 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).

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, the presence of an opioid appeared to increase exposure by about 11 %.

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 covariants 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.

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

Hepatic impairment: Erlotinib is primarily cleared by the liver. In patients with solid tumours and with moderately impaired hepatic function (Child-Pugh score 7-9), geometric mean erlotinib AUC_{0-t} and C_{max} was 27000 ng•h/mL and 805 ng/mL, respectively, as compared to 29300 ng•h/mL and 1090 ng/mL in patients with adequate hepatic function including patients with primary liver cancer or hepatic metastases. Although the C_{max} was statistically significant lower in moderately hepatic impaired patients, this difference is not considered clinically relevant. No data are available regarding the influence of severe hepatic dysfunction on the pharmacokinetics of erlotinib. In population pharmacokinetic analysis, increased serum concentrations of total bilirubin were associated with a slower rate of erlotinib clearance.

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

5.3 Preclinical safety data

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

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

Erlotinib tested negative in conventional genotoxicity studies. Carcinogenicity studies have not been performed.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate

Cellulose, microcrystalline (E460)

Sodium starch glycolate Type A

Sodium laurilsulfate
Magnesium stearate (E470 b)

Tablet coat:

Hydroxypropyl cellulose (E463)
Titanium dioxide (E171)
Macrogol
Hypromellose (E464)

Printing ink brown

Shellac (E904)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC blister sealed with aluminium foil containing 30 tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/311/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 September 2005

10. DATE OF REVISION OF THE TEXT

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Roche Pharma AG
Emil-Barell-Strasse 1
D-79639 Grenzach-Wyhlen
Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2)

• **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

• **OTHER CONDITIONS**

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1.1 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tarceva 25 mg film-coated tablets
Erlotinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 25 mg of erlotinib (as erlotinib hydrochloride).

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/311/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tarceva 25 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Tarceva 25 mg film-coated tablets
Erlotinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tarceva 100 mg film-coated tablets
Erlotinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg of erlotinib (as erlotinib hydrochloride).

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/311/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tarceva 100 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Tarceva 100 mg film-coated tablets
Erlotinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tarceva 150 mg film-coated tablets
Erlotinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg of erlotinib (as erlotinib hydrochloride).

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/311/003

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tarceva 150 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Tarceva 150 mg film-coated tablets
Erlotinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Tarceva 25 mg Film-Coated Tablets **Tarceva 100 mg Film-Coated Tablets** **Tarceva 150 mg Film-Coated Tablets** Erlotinib

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Tarceva is and what it is used for
2. Before you take Tarceva
3. How to take Tarceva
4. Possible side effects
5. How to store Tarceva
6. Further information

1. WHAT IS TARCEVA AND WHAT IT IS USED FOR

Tarceva is a medicinal product used to treat cancer by preventing the activity of a protein called epidermal growth factor receptor. This protein is known to be involved in the growth and spread of cancer cells.

This medicine can be prescribed to you if you have non-small cell lung cancer at an advanced stage. It can be prescribed either if your disease remains largely unchanged after initial chemotherapy, or if previous chemotherapy has not helped to stop your disease.

This medicine can also be prescribed to you in combination with another treatment called gemcitabine if you have cancer of the pancreas at a metastatic stage.

2. BEFORE YOU TAKE TARCEVA

You should not take Tarceva:

- if you are allergic (hypersensitive) to erlotinib or to any of the ingredients of Tarceva.

Take special care during treatment with Tarceva:

- if you are taking other medicines that may increase or decrease the amount of erlotinib in your blood (for example antifungals like ketoconazole, protease inhibitors, erythromycin, clarithromycin, phenytoin, carbamazepine, barbiturates, rifampicin, ciprofloxacin, omeprazole, ranitidine or St. John's Wort). In some cases these medicines may reduce the efficacy or increase the side effects of Tarceva and your doctor may need to adjust your treatment. Your doctor might avoid treating you with these medicines while you are receiving Tarceva.
- if you take blood thinners (like warfarin or other coumarin-derivatives) because Tarceva may increase your risk of bleeding and your doctor will need to regularly monitor you with blood tests.

See also below "Taking other medicines".

You should tell your doctor:

- if you have sudden difficulty in breathing associated with cough or fever because your doctor may need to treat you with other medicines and interrupt your Tarceva treatment;
- if you have diarrhoea because your doctor may need to treat you with anti-diarrhoeal (for example loperamide);
- immediately, if you have severe or persistent diarrhoea, nausea, loss of appetite, or vomiting because your doctor may need to interrupt your Tarceva treatment and may need to treat you in the hospital.
- if you have severe pain in the abdomen, severe blistering or peeling of skin, or acute or worsening eye problems (for example eye pain). Your doctor may need to interrupt or stop your treatment.

See also section 4 “Possible side effects”.

It is not known whether Tarceva has a different effect if your liver or kidneys are not functioning normally. The treatment with this medicine is not recommended if you have a severe liver disease or severe kidney disease.

Your doctor must treat you with caution if you have a glucuronidation disorder like Gilbert’s syndrome.

You are advised to stop smoking if you are treated with Tarceva as smoking could decrease the amount of your medicine in the blood.

Taking other medicines:

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Tarceva with food and drink:

Do not take Tarceva with food.

Children and adolescents

Tarceva has not been studied in patients under the age of 18 years. The treatment with this medicine is not recommended for children and adolescents.

Pregnancy and breast-feeding

Avoid pregnancy while being treated with Tarceva. If you could become pregnant use adequate contraception during treatment, and for at least 2 weeks after taking the last tablet.

If you become pregnant while you are being treated with Tarceva, immediately inform your doctor who will decide if the treatment should be continued.

Ask your doctor or pharmacist for advice before taking any medicine.

Do not breast-feed if you are being treated with Tarceva.

Driving and using machines:

Tarceva has not been studied for its possible effects on the ability to drive and use machines but it is very unlikely that your treatment will affect this ability.

Important information about some of the ingredients of Tarceva:

Tarceva contains a sugar called lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking Tarceva.

3. HOW TO TAKE TARCEVA

Always take Tarceva exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The tablet should be taken at least one hour before or two hours after the ingestion of food.

The usual dose is one tablet of Tarceva 150 mg each day if you have non-small cell lung cancer.

The usual dose is one tablet of Tarceva 100 mg each day if you have metastatic pancreatic cancer. Tarceva is given in combination with gemcitabine treatment.

Your doctor may adjust your dose in 50 mg steps. For the different dosage regimens Tarceva is available in strengths of 25 mg, 100 mg or 150 mg.

If you take more Tarceva than you should:

Contact your doctor or pharmacist immediately.

You may have increased side effects and your doctor may interrupt your treatment.

If you forget to take Tarceva:

If you miss one or more doses of Tarceva, contact your doctor or pharmacist as soon as possible.

Do not take a double dose to make up for a forgotten dose.

If you stop taking Tarceva:

It is important to keep taking Tarceva every day, as long as your doctor prescribes it for you.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Tarceva can cause side effects.

Very common side effects (occurring in more than 1 out of 10 patients) are rash and diarrhoea as well as itching, dry skin, loss of hair, eye irritation due to conjunctivitis/keratoconjunctivitis, loss of appetite, decreased weight, nausea, vomiting, mouth irritation, stomach pain, indigestion, flatulence, tiredness, fever, rigors, difficulty in breathing, cough, infection, headache, altered skin sensation or numbness in the extremities, depression and abnormal blood tests for the liver function. In rare cases (occurring in less than 1 out of 1000 patients), liver failure was observed. If your blood tests indicate severe changes in your liver function, your doctor may need to interrupt your treatment. Persistent and severe diarrhoea may lead to low blood potassium and kidney failure, particularly if you receive other chemotherapy treatments at the same time. If you experience more severe or persistent diarrhoea contact your doctor immediately as your doctor may need to treat you in the hospital.

Rash may occur or worsen in sun exposed areas. If you are exposed to sun, protective clothing, and/or use of sun screen (e.g. mineral-containing) may be advisable.

Common side effects (occurring in less than 1 out of 10 patients) are bleeding from the stomach or the intestines and bleeding from the nose, and eye irritation due to keratitis.

Contact your doctor as soon as possible if you suffer from any of the above side effects. In some cases your doctor may need to reduce your dose of Tarceva or interrupt treatment.

An uncommon serious side effect (occurring in less than 1 out of 100 patients) is a rare form of lung irritation called interstitial lung disease. This disease can also be linked to the natural progression of your medical condition and can have a fatal outcome in some cases. If you develop symptoms such as sudden difficulty in breathing associated with cough or fever **contact your doctor immediately** as you could suffer from this disease. Your doctor may decide to permanently stop your treatment with Tarceva.

Hair and nail changes have been observed. These cases were mostly non-serious. They included inflammatory reactions around the fingernail (common), excess body and facial hair of a male distribution pattern (uncommon), eyelash and eyebrow changes (uncommon), and brittle and loose nails (uncommon).

Uncommonly (occurring in less than 1 out of 100 patients), gastrointestinal perforations have been observed. Tell your doctor if you have severe pain in your abdomen. Also, tell your doctor if you had peptic ulcers or diverticular disease in the past, as this may increase this risk.

The following side effects have been observed very rarely (in less than 1 out of 10'000 patients): cases of ulceration or perforation of the cornea, severe blistering or peeling of skin (suggestive of Stevens-Johnson syndrome).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. STORING TARCEVA

Keep out of the reach and sight of children.

Do not use Tarceva after the expiry date which is stated on the blister and the carton after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Tarceva contains:

- **The active substance** of Tarceva is erlotinib. Each film-coated tablet contains 25 mg, 100 mg or 150 mg of erlotinib (as erlotinib hydrochloride) depending on the strength.
- **The other ingredients** are:
 - Tablet core: lactose monohydrate, cellulose microcrystalline, sodium starch glycolate type A, sodium laurilsulfate, magnesium stearate.
 - Tablet coat: hypromellose, hydroxypropyl cellulose, titanium dioxide, macrogol.
 - Printing ink:
 - Tarceva 25 mg: shellac, iron oxide yellow
 - Tarceva 100 mg: shellac, iron oxide yellow, iron oxide black, titanium dioxide
 - Tarceva 150 mg: shellac, iron oxide red

What Tarceva looks like and contents of the pack:

Tarceva 25 mg is supplied as a white to yellowish, round, film-coated tablet with 'Tarceva 25' and logo printed in brownish yellow on one side and is available in pack sizes of 30 tablets.

Tarceva 100 mg is supplied as a white to yellowish, round, film-coated tablet with 'Tarceva 100' and logo printed in grey on one side and is available in pack sizes of 30 tablets.

Tarceva 150 mg is supplied as a white to yellowish, round, film-coated tablet with 'Tarceva 150' and logo printed in brown on one side and is available in pack sizes of 30 tablets.

Marketing Authorisation Holder and Manufacturer:

Marketing Authorisation Holder:

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Manufacturer:

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last approved in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.emea.europa.eu/>.