SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Tarceva® 25 mg tablets

Tarceva® 100 mg tablets

Tarceva® 150 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains erlotinib hydrochloride equivalent to 25 mg, 100 mg or 150 mg erlotinib.

Excipients with known effect: Lactose monohydrate.

Contains sugar, i.e. lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tarceva 25 mg: White to yellowish, round, biconvex tablets with ‘T25’ engraved on one side.

Tarceva 100 mg: White to yellowish, round, biconvex tablets with ‘T100’ engraved on one side.

Tarceva 150 mg: White to yellowish, round, biconvex tablets with ‘T150’ engraved on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Non-Small Cell Lung Cancer (NSCLC)

Tarceva is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer with EGFR activating mutation after failure of at least one prior chemotherapy regimen. Tarceva was not effective after platinum-based therapy that included gemcitabine.

Tarceva monotherapy is indicated for the maintenance treatment of patients having received first-line platinum-based (other than gemcitabine + cisplatin) doublets chemotherapy for locally advanced or metastatic NSCLC.

No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with EGFR-negative tumours. See section 5.1.

Bronchial Adenocarcinoma

Tarceva is indicated for the first-line treatment of patients with locally advanced or metastatic (stage 4) bronchial adenocarcinoma whose tumours have demonstrated EGFR activating mutations and who have never smoked and had ECOG performance status of 0 – 1.

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 first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.

4.2 Posology and method of administration

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

Concomitant use of CYP3A4 substrates and modulators may require dose adjustment. See section 4.5. Where dose adjustment is necessary, reduce in 50 mg steps.

Non-Small Cell Lung Cancer and Bronchial Adenocarcinoma:

EGFR mutation testing should be performed prior to initiation of Tarceva therapy in chemo-naive patients with advanced or metastatic NSCLC and bronchial adenocarcinoma.

The recommended dose is 150 mg daily taken at least 1 hour before or two hours after the ingestion of food. Where dose adjustment is necessary, reduce in 50 mg steps.

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 gemcitabine package insert for pancreatic cancer indication).

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. See section 5.2. Tarceva should not be used in patients with severe hepatic dysfunction (AST/SGOT and ALT/SGPT > 5 x ULN). Dose reduction or interruption of Tarceva should be considered if severe adverse reactions occur. Safety and efficacy have not been studied in patients with severe hepatic dysfunction.

Renal impairment: The safety and efficacy of Tarceva has not been studied in patients with renal impairment. See section 5.2. Tarceva should not be used in patients with severe renal impairment.

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

Smokers: Cigarette smoking has been shown to reduce erlotinib exposure by 50 - 60 %. The maximum tolerated dose of Tarceva in NSCLC and bronchial adenocarcinoma patients who currently smoke cigarettes was 300 mg. The 300 mg dose did not show improved efficacy in second line treatment after failure of chemotherapy compared to the recommended 150 mg dose in patients who continue to smoke cigarettes.

4.3 Contraindications

Severe hypersensitivity to erlotinib or to any of the excipients. Patients with a history of or hereditary galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption.

4.4 Special warnings and precautions for use

Interstitial Lung Disease: Cases of interstitial lung disease (ILD)-like events, including fatalities, have been reported uncommonly in patients receiving Tarceva for treatment of non-small cell lung cancer (NSCLC), pancreatic cancer or other advanced solid tumours. In the pivotal study BR.21 in NSCLC, the incidence of ILD-like events was (0,8 %) the same in both the placebo and the 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 %. Some examples of 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, alveolitis and lung infiltration. These ILD-like events started from a few days to several months after initiating Tarceva therapy. Most of the cases were associated with confounding or contributing factors such as concomitant or prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease or pulmonary infections.

In patients who develop acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnoea, cough and fever, Tarceva therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, Tarceva should be discontinued and appropriate treatment administered as necessary. See section 4.8.

Diarrhoea, Dehydration, Electrolyte Imbalance and Renal Failure: Diarrhoea has occurred in approximately 50 % of patients on Tarceva and moderate or severe diarrhoea should be treated, e.g. with loperamide. In some cases dose reduction may be necessary. 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 reports of hypokalaemia and renal failure (including fatalities). Some reports of renal failure were secondary to severe dehydration due to diarrhoea, vomiting and/or anorexia while others were confounded by concomitant chemotherapy. In more severe or persistent cases of diarrhoea, or cases leading to dehydration, particularly in patients with aggravating risk factors (concomitant medications, symptoms or diseases or other predisposing conditions including advanced age), Tarceva therapy should be interrupted and appropriate measures should be taken to intensively rehydrate the patients intravenously. In addition, renal function and serum electrolytes including potassium should be monitored in patients at risk of dehydration.

Hepatitis, hepatic failure: Cases of hepatic failure (including fatalities) have been reported during use of Tarceva. Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medicines. Therefore, in such patients, periodic liver function testing should be considered. Tarceva dosing should be interrupted if changes in liver function are severe. Tarceva is not recommended for use in patients with severe hepatic dysfunction.

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

Bullous and exfoliative skin disorders: Bullous, blistering and exfoliative skin conditions have been reported, including cases of Stevens-Johnson syndrome/toxic epidermal necrolysis, which in some cases were fatal. Tarceva treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions.

For patients who are exposed to sun, protective clothing, and/or use of sun screen (e.g. mineral-containing) may be advisable.

Ocular Disorders: Cases of corneal perforation or ulceration, uveitis, iridocyclitis and iritis 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.

Smokers:

Current smokers should be advised to stop smoking, as plasma concentrations of erlotinib in smokers as compared to non-smokers are reduced. The degree of reduction is likely to be clinically significant (see sections 4.2, 4.5, 5.1 and 5.2).

Interactions with other medicines:

Potential 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).

Other forms of interactions:

Erlotinib is characterised by a decrease in solubility above 5. Medicines that alter pH of the upper gastrointestinal tract (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 co-administered with such agents is not likely to compensate for the loss of exposure. Combination of erlotinib with proton pump inhibitors should be avoided. The effects of concomitant administration of erlotinib with H2 antagonists and antacids are unknown; however, reduced bioavailability is likely. Therefore, concomitant administration of these combinations should be avoided (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.

Tarceva tablets contain lactose and should not be administered to patients with a history of or hereditary, galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption. See section 4.3.

In order to improve traceability of biological medicines, the Tarceva should be clearly recorded in the patient file. Substitution by any other biological medicine requires the consent of the

prescribing doctor, and the substitute medicine to be recorded in the files. Information as set forth in this package insert only applies to Tarceva.

4.5 Interaction with other medicines 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 co-administration 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 medicines 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 or combined CYP3A4/CYP1A2 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, following a 150 mg dose of Tarceva, as compared to Tarceva alone. Pre-treatment and co-administration of rifampicin with a single 450 mg dose of Tarceva resulted in a mean erlotinib exposure (AUC) of 57,5 % of that after a single 150 mg Tarceva dose in the absence of rifampicin treatment. Co-administration of Tarceva with CYP3A4 inducers should therefore be avoided. Alternative treatments lacking potent CYP3A4 inducing activity should be considered when possible. For patients who require concomitant treatment with Tarceva and a potent CYP3A4 inducer such as rifampicin an increase in dose to 300 mg should be considered while their safety (including renal and liver functions and serum electrolytes) is closely monitored, and if well tolerated for more than 2 weeks, further increase to 450 mg could be considered with close safety monitoring. Higher doses have not been studied in this setting.

Reduced exposure may also occur with other inducers e.g. phenytoin, carbamazepine, barbiturates or St. Johns Wort (*hypericum perforatum*). Caution should be observed when these

active substances are combined with erlotinib. Alternate treatments lacking potent CYP3A4 inducing activity should be considered when possible.

Interactions with warfarin, leading to increased International Normalised Ratio (INR) and bleeding events, which in some cases were fatal have been reported in patients receiving Tarceva. Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR.

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

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).

Efficacy in smoking patients has not been established.

Smokers should be advised to stop smoking as cigarette smoking, which is known to induce CYP1A1 and CYP1A2, has been shown to reduce erlotinib exposure by 50 – 60 % (see section 4.2, 4.4, 5.1 and 5.2).

Erlotinib is a substrate for the P-glycoprotein active substance transporter. Concomitant administration of inhibitors of Pgp, e.g. ciclosporin and verapamil, may lead to altered distribution and/or altered elimination of erlotinib. The consequences of this interaction for e.g. CNS toxicity have not been established. Caution should be exercised in such situations.

Erlotinib is characterised by a decrease in solubility at pH above 5. 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. Therefore, medicines that alter the pH of the upper GI tract may alter the solubility of erlotinib and hence its bioavailability. Increasing the dose of Tarceva when co-administered with such medicines is not likely to compensate for this loss of exposure. The effect of antacids and H2 antagonists on the absorption of erlotinib have not been investigated but absorption may be impaired, leading to lower plasma levels. Combination of erlotinib with proton pump inhibitors should be avoided. The effects of concomitant administration of erlotinib with H2 antagonists and

antacids are unknown; however, reduced bioavailability is likely. Therefore, concomitant administration of these combinations should be avoided. If the use of antacids is considered necessary during treatment with 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. erlotinib must be taken at least 2 hours before or 10 hours after the ranitidine dosing. The ranitidine dose should be divided into 2 equal doses per day.

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 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

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. Women who are pregnant and/or breastfeeding should not receive Tarceva.

Pregnancy

There are no studies in pregnant and/or breastfeeding women using Tarceva. Studies in animals have shown no evidence of teratogenicity or abnormal parturition. However, an adverse effect on the pregnancy can not be excluded as rat and rabbit studies have shown increased embryo/foetal lethality. The potential risk for humans is unknown.

Breastfeeding

It is not known whether erlotinib is excreted in human milk. No studies have been conducted to assess the impact of Tarceva on milk production or its presence in breast milk. As the potential harm to the nursing infant is unknown, mothers should be advised against breastfeeding while receiving Tarceva and for at least 2 weeks after the final dose.

Fertility

Studies in animals have shown no evidence of impaired fertility. However, an adverse effect on the fertility cannot be excluded as animal studies have shown effects on reproductive parameters. The potential risk for humans is unknown.

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, Tarceva is not associated with impairment of mental ability.

4.8 Undesirable effects

Tarceva monotherapy: The following side effects/adverse events have been observed in clinical studies with bronchial adenocarcinoma. In a randomised, double-blind study (BR.21: Tarceva administered as second-line therapy), rash (75 %) and diarrhoea (54 %) were the most frequent side effects regardless of causality. 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.

Skin fissures, mostly non-serious, were reported, most were associated with rash and dry skin.

Side effects occurring more frequently (≥ 3 %) in Tarceva-treated patients than in the placebo group, 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 below.

Table 1: Side effects occurring more frequently (≥ 3 %) in the Tarceva group than in the placebo group and in ε 10 % of patients in the Tarceva group

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

Skin and subcutaneous tissue disorders						
Rash***	75	8	< 1	17	0	0
Pruritus	13	< 1	0	5	0	0
Dry skin	12	0	0	4	0	0
General disorders and administration site conditions						
Fatigue	52	14	4	45	16	4

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

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

*** Rash included dermatitis acneiform

In two other double-blind, randomised, placebo-controlled Phase III studies (BO18192, SATURN and B025460, IUNO) Tarceva was administered as maintenance after first-line chemotherapy. SATURN and IUNO were conducted in a total of 1 532 patients with advanced, recurrent or metastatic NSCLC following first-line standard platinum-based chemotherapy; no new safety signals were identified.

The most frequent side effects seen in patients treated with Tarceva in studies BO18192 and B025460 were rash and diarrhoea (see table 2). No Grade 4 rash or diarrhoea was observed in either study. Rash and diarrhoea resulted in discontinuation of Tarceva in 1 % and < 1 % of patients, respectively, in study B018192, while no patient discontinued for rash or diarrhoea in B025460. Dose modifications (interruptions or reductions) for rash and diarrhoea were needed in 8,3 % and 3 % of patients, respectively, in study B018192 and 5,6 % and 2,8 % of patients, respectively in B025460.

Table 2: Side effect table for the most frequent side effects in B018192 (SATURN) and B025460 (IUNO).

	B018192 (SATURN)*	**B025460 (IUNO)***

MedRA Preferred Term	Tarceva n = 433	Placebo n = 445	Tarceva n = 322	Placebo n = 319
	%	%	%	%
Rash, all grades	49,2	5,8	39,4	10,0
Grade 3	6,0	0	5,0	1,6
Diarrhoea, all grades	20,3	4,5	24,2	4,4
Grade 3	1,8	0	2,5	0,3

*Safety analysis population

In an open-label, randomised phase III study, ML 20650 conducted in 154 patients, the safety of Tarceva for first-line treatment of bronchial adenocarcinoma patients with EGFR activating mutations was assessed in 75 patients; no new safety signals were observed in these patients. The most frequent side effects seen in patients treated with Tarceva in study ML20650 were rash and diarrhoea (any Grade 80 % and 57 %, respectively), most were Grade 1/2 in severity and manageable without intervention. Grade 3 rash and diarrhoea occurred in 9 % and 4 % of patients, respectively. No Grade 4 rash or diarrhoea was observed. Both rash and diarrhoea resulted in discontinuation of Tarceva in 1 % of patients. Dose modifications (interruptions or reductions) for rash and diarrhoea were needed in 11 % and 7 % of patients, respectively.

Tarceva in combination with chemotherapy for pancreatic carcinoma

The side effects listed in table 3 below are based on data from the controlled clinical trial, PA.3, where 259 patients with pancreatic cancer received Tarceva 100 mg plus gemcitabine compared to 256 patients in the placebo plus gemcitabine-arm.

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

The Tarceva 150 mg plus gemcitabine cohort (23 patients) was associated with a higher rate of certain class-specific side effects including rash and required more frequent dose reduction or interruption.

Table 3: Side effects occurring ≥ 10 % and more frequently (≥ 3 %) in Tarceva 100 mg plus gemcitabine-treated patients than in placebo plus gemcitabine group in study PA.3.

	Erlotinib N = 259			**Placebo N = 256**		
NCI-CTC Grade	**Any Grade**	**3**	**4**	**Any Grade**	**3**	**4**
MedDRA Preferred Term	**%**	**%**	**%**	**%**	**%**	**%**
Total patients with any AE	99	48	22	97	48	16
Infections and infestations						
Infection*	31	3	< 1	24	6	< 1
Metabolism and nutrition disorders						
Decreased weight	39	2	0	29	< 1	0
Psychiatric disorders						
Depression	19	2	0	14	< 1	0
Nervous system disorders						
Headache	15	< 1	0	10	0	0
Neuropathy	13	1	< 1	10	< 1	0
Respiratory ,thoracic and mediastinal disorders						
Cough	16	0	0	11	0	0
Gastrointestinal disorders						

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
Skin and subcutaneous tissue disorders						
Rash***	69	5	0	30	1	0
Alopecia	14	0	0	11	0	0
General disorders and administration site conditions						
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, hypokalaemia and renal failure.

*** Rash included dermatitis acneiform

Other Observations:

Safety evaluation of Tarceva is based on the data from more than 1 200 patients treated with at least one dose of Tarceva 150 mg monotherapy and more than 300 patients who received Tarceva 100 mg or 150 mg in combination with gemcitabine.

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

The following side effects have been observed in patients who received Tarceva as a single agent and patients who received Tarceva concurrently with chemotherapy.

Very common side effects (≥1/10), are presented in Tables 3 and 4. Side effects in other frequency categories are summarised below.

Gastrointestinal disorders:

Common: Gastrointestinal bleeding, including fatalities. 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, including fatalities.

Skin and subcutaneous tissue disorders:

Common: Alopecia. Paronychia. Dry skin. Rash, as mild to moderate. Acne, dermatitis acneiform and folliculitis, as mild to moderate and non-serious.

Uncommon Hirsutism, eyebrow changes and brittle and loose nails. Mild skin reactions such as hyperpigmentation.

Very rare: Bullous, blistering and exfoliative skin conditions including cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which may be 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: 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 and conjunctivitis.

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

Very rare: Corneal ulcerations and perforations have been reported very rarely in patients receiving Tarceva as a complication of mucocutaneous inflammation. Cases of uveitis have been reported.

Respiratory, thoracic and mediastinal disorders:

Common: Epistaxis

Uncommon: Serious interstitial lung disease (ILD), including fatalities, in patients receiving Tarceva

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Report Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Single oral doses of Tarceva up to 1 000 mg in healthy subjects, and up to 1 600 mg in given as a single dose once weekly cancer patients have been tolerated. Repeated twice daily doses of 200 mg in healthy subjects were poorly tolerated after only a few days of dosing. Based on the data from these studies, severe adverse events such as diarrhoea, rash and possibly liver transaminase elevation may occur above the recommended dose. In case of suspected overdose Tarceva should be withheld and symptomatic treatment initiated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent protein kinase inhibitor, ATC code: L01XE03.

Mechanism of Action: Erlotinib inhibits the intracellular phosphorylation of HER1/EGFR (epidermal growth factor receptor type 1, also known as HER1). HER1/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.

5.2 Pharmacokinetic properties

Absorption: Oral erlotinib is absorbed after oral administration and has an extended absorption phase, with mean peak plasma levels occurring at approximately 4 hours after oral dosing. A study in normal healthy volunteers provided an estimate oral bioavailability of 59 % compared to IV administration. The exposure after an oral dose may be increased by food. Following absorption, erlotinib is highly bound in blood, with approximately 95 % bound to blood components, primarily to plasma proteins (i.e. albumin and alpha-1 acid glycoprotein [AAG]), with a free fraction of approximately 5 % at the recommended dose. Following a 150 mg oral dose of erlotinib, at steady state, the median time to reach maximum plasma concentrations is approximately 4,0 hours with median maximum plasma concentrations achieved of 1,995 ng/mL. Prior to the next dose at 24 hours, the median minimum plasma concentrations are 1,238 ng/mL. Median AUC achieved during the dosing interval at steady state are 41,300 µg*hr/mL.

Distribution: Erlotinib has a mean apparent volume of distribution of 232 L. Erlotinib distributes into tumour tissue of humans. In a study of 4 patients (3 with non-small cell lung cancer [NSCLC], and 1 with laryngeal cancer) receiving 150 mg daily oral doses of erlotinib, tumour samples from surgical excisions on Day 9 of treatment revealed tumour concentrations of erlotinib that varied widely but averaged 1,185 ng/g of tissue.

This corresponded to an overall average of 63 % of the steady state observed peak plasma concentrations. The primary active metabolites were present in tumours at concentrations averaging 160 ng/g tissue, which corresponded to an overall average of 113 % of the observed steady state peak plasma concentrations. Plasma protein binding is approximately 95 %. Erlotinib binds to serum albumin and alpha-1 acid glycoprotein (AAG).

Biotransformation: Erlotinib is metabolised in humans by hepatic cytochrome P450 enzymes, primarily CYP3A4, and to a lesser extent by CYP1A2. Extrahepatic metabolism by CYP3A4 in the intestine, CYP1A1 in lung and CYP1B1 in tumour tissue potentially contribute to the metabolic clearance of erlotinib. *In vitro* studies indicate approximately 80 – 95 % of erlotinib metabolism is by the CYP3A4 enzyme. There are three main metabolic pathways identified:

1) O-demethylation of either side chain or both, followed by oxidation to the carboxylic acids;

2) oxidation of the acetylene moiety followed by hydrolysis to the aryl carboxylic acid; and

3) aromatic hydroxylation of the phenyl-acetylene moiety.

The primary metabolites of erlotinib produced by O-demethylation of either side chain have comparable potency to erlotinib in preclinical *in vitro* assays and *in vivo* tumour models. They are present at levels that are less than 10 % of erlotinib and display similar pharmacokinetics as erlotinib.

Elimination: The metabolites and trace amounts of erlotinib are excreted predominantly via the faeces (more than 90 %), with renal elimination accounting for only a small amount of an oral dose.

A population pharmacokinetic analysis in 591 patients receiving single agent Tarceva show a mean apparent clearance of 4,47 L/hour with a median half-life of 36,2 hours. Therefore, the time to reach steady state plasma concentration would be expected to occur in approximately 7 – 8 days. No significant relationships between predicted apparent clearance and patient age, body weight, gender, and ethnicity were observed.

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

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

Pharmacokinetics in special populations:

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

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

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

Smokers: A pharmacokinetic study in nonsmoking and currently cigarette smoking healthy subjects has shown that cigarette smoking leads to increased clearance of, and decreased exposure to, erlotinib. The $AUC_{0\text{-infinity}}$ in smokers was about 1/3 of that in never/former smokers (n = 16 in each of smoker and never/former smoker arms). This reduced exposure in current smokers is presumably due to induction of CYP1A1 in lung and CYP1A2 in the liver.

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).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropyl cellulose, hydroxypropyl methyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium lauryl sulphate, sodium starch glycolate and titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

Keep out of reach of children.

Do not store above 30 °C.

6.5 Nature and contents of container

Tarceva 25 mg: Alu/PVC (transparent) blisters containing 30 tablets per pack

Tarceva 100 mg: Alu/PVC (transparent) blisters containing 30 tablets per pack

Tarceva 150 mg: Alu/PVC (transparent) blisters containing 30 tablets per pack

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road, Hertford Office Park,

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South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBER(S)

Tarceva® 25 mg Tablets A40/26/0359

Tarceva® 100 mg Tablets A40/26/0360

Tarceva® 150 mg Tablets A40/26/0361

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration: 17 April 2009

10. DATE OF REVISION OF THE TEXT

Last revision: 07 March 2022

	Tarceva 100 mg	Tarceva 150 mg
Namibia:	NS2 19/26/0060	NS2 19/26/0061

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