

Data Sheet

Tarceva[®]

Erlotinib hydrochloride 25 mg, 100 mg, 150 mg film-coated tablets

Antineoplastic agent

Pharmaceutical Form

Film-coated tablets.

Qualitative and Quantitative Composition

Active ingredient

Erlotinib

One film-coated tablet of each strength contains erlotinib hydrochloride, corresponding to 25 mg, 100 mg and 150 mg of erlotinib.

Excipients

Tablet core:

Lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulphate, magnesium stearate.

Tablet coat:

Hydroxypropyl cellulose, titanium dioxide, polyethylene glycol, hydroxypropyl methylcellulose.

Printing ink:

Shellac, iron oxide yellow, anhydrous ethanol, N-butyl alcohol, isopropyl alcohol, ethyl acetate.

The 100 mg tablets also contain titanium dioxide and iron oxide black.

The 150 mg tablets also contain iron oxide black and iron oxide red.

Appearance

Tarceva 25 mg tablets are round, biconvex, white to yellowish tablets marked with *TARCEVA 25* and *logo* in brownish-yellow on one side.

Tarceva 100 mg film-coated tablets are round, biconvex, white to yellowish tablets marked with *TARCEVA 100* and *logo* in grey on one side.

Tarceva 150 mg film-coated tablets are round, biconvex, white to yellowish tablets marked with *TARCEVA 150* and *logo* in brown on one side.

Clinical Particulars

Therapeutic Indications

Non-small cell lung cancer

Tarceva is indicated for maintenance therapy in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not progressed on first-line chemotherapy. Efficacy is influenced by tumour characteristics (see Clinical/efficacy studies).

Tarceva is also indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have previously received chemotherapy.

Pancreatic cancer

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

Dosage and Method of Administration

Standard dosage

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 gemcitabine prescribing information for the correct dosage of gemcitabine in pancreatic cancer).

Special Dosage Instructions

Concomitant use of CYP 3A4 substrates and modulators may require dose adjustment (see Interactions with other Medicinal Products and other Forms of Interaction).

When dose adjustment is necessary, it is recommended to reduce the dose in 50 mg increments (see Interactions with other Medicinal Products and other Forms of Interaction).

Hepatic impairment: Erlotinib is eliminated by hepatic metabolism and biliary excretion. Although erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh score 7-9) compared with patients with adequate hepatic function, caution should be used when administering Tarceva to patients with hepatic impairment. Dose reduction or interruption of Tarceva should be considered if severe adverse reactions occur.

Safety and efficacy have not been studied in patients with severe hepatic impairment (see Warnings and Precautions, Pharmacokinetics in Special Populations).

Renal impairment: The safety and efficacy of Tarceva has not been studied in patients with renal impairment (see Pharmacokinetics in Special Populations).

Paediatric use: The safety and efficacy of Tarceva has not been studied 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 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 Interactions with other Medicinal Products and other Forms of Interaction, Pharmacokinetics in Special Populations).

Contraindications

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

Warnings and Precautions

General

Interstitial lung disease

Cases of interstitial lung disease (ILD)-like events, including fatalities, have been reported uncommonly in patients receiving Tarceva for treatment of non-small cell lung cancer (NSCLC), pancreatic cancer or other advanced solid tumours. In the pivotal study BR.21 in NSCLC, the incidence of serious ILD-like events was 0.8% in each of the placebo and Tarceva arms. In 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 patients treated with Tarceva 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 include pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome, lung infiltration and alveolitis. 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 and/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 initiated as necessary (see Undesirable Effects).

Diarrhoea, dehydration, electrolyte imbalance and renal failure

Diarrhoea has occurred in patients on Tarceva and moderate or severe diarrhoea should be treated 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 Undesirable Effects).

There have been rare 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 groups of patients with aggravating risk

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

Hepatitis, hepatic failure

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

Gastrointestinal perforation

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

Bullous and exfoliative skin disorders

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

Ocular disorders

Very rare cases of corneal perforation or ulceration have been reported during use of 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 Undesirable Effects).

Interactions

Tarceva has a potential for clinically significant medicine interactions (see Interactions with other Medicinal Products and other Forms of Interaction).

Ability to Drive and Use Machines

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

Interactions with other Medicinal Products and other Forms of Interaction

Erlotinib is metabolised in the liver by the hepatic cytochromes in humans, primarily CYP3A4 and to a lesser extent by CYP1A2 and the pulmonary isoform CYP1A1. Potential interactions may occur with medicines which are metabolised by, or are inhibitors or inducers of, these enzymes.

Potent inhibitors of CYP3A4 activity decrease erlotinib metabolism and increase erlotinib plasma concentrations. Inhibition of CYP3A4 metabolism by ketoconazole (200 mg orally bd for 5 days) resulted in increased exposure to erlotinib (86% in median erlotinib exposure [AUC]) and a 69% increase in maximum concentration (C_{max}) when compared to erlotinib alone. When Tarceva was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2, the erlotinib exposure

[AUC] and C_{max} increased by 39% and 17%, respectively. Therefore caution should be used when administering Tarceva with potent CYP3A4 (or combined CYP3A4/CYP1A2) inhibitors. In these situations, the dose of Tarceva should be reduced if toxicity is observed.

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

Pre-treatment and co-administration of rifampicin with a single 450 mg dose of Tarceva resulted in a decreased mean erlotinib exposure [AUC], which was 57.5% of a single 150 mg Tarceva dose in the absence of rifampicin treatment. Alternative treatments lacking potent CYP3A4 inducing activity should be considered when possible. For patients who require concomitant treatment with Tarceva and a potent CYP3A4 inducer such as rifampicin, an increase in dose to 300 mg should be considered while their safety is closely monitored and if well tolerated for more than 2 weeks, a further increase to 450 mg could be considered with close safety monitoring. Higher doses have not been studied in this setting.

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

The solubility of erlotinib is pH dependent. Erlotinib solubility decreases as pH increases. Medicines that alter the pH of the upper gastrointestinal tract may alter the solubility of erlotinib and hence its bioavailability. Co-administration of Tarceva with omeprazole, a proton pump inhibitor, decreased the erlotinib exposure [AUC] and 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 H_2 -receptor antagonist, decreased erlotinib exposure [AUC] and C_{max} by 33% and 54%, respectively. Therefore, co-administration of medicines that reduce gastric acid production with Tarceva should be avoided where possible. Increasing the dose of Tarceva when co-administered with such agents is not likely to compensate for this loss of exposure. However, when Tarceva was dosed in a staggered manner 2 hours before or 10 hours after ranitidine 150 mg bd, erlotinib exposure [AUC] and C_{max} decreased only by 15% and 17%, respectively. If patients need to be treated with such medicines, then an H_2 -receptor antagonist such as ranitidine should be considered and used in a staggered manner. Tarceva must be taken at least 2 hours before or 10 hours after the H_2 -receptor antagonist dosing.

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

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

Smokers should be advised to stop smoking as cigarette smoking, which is known to induce CYP1A1 and CYP1A2, has been shown to reduce erlotinib exposure by 50 - 60% (see Special Dosage Instructions, Pharmacokinetics in Special Populations).

In a phase Ib study, there were no significant effects of gemcitabine on the pharmacokinetics of erlotinib nor were there significant effects of erlotinib on the pharmacokinetics of gemcitabine.

Use in Special Populations

Pregnancy

There are no adequate or well controlled studies in pregnant women using Tarceva. Studies in animals have shown some reproductive toxicity (see Preclinical Safety). 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.

Nursing mothers

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.

Hepatic impairment

Erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh score 7 - 9) compared with patients with adequate hepatic function, including patients with primary liver cancer or hepatic metastases. Safety and efficacy have not been studied in patients with severe hepatic impairment. (see Warnings and Precautions – Hepatitis, hepatic failure).

Undesirable Effects

Clinical trials

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

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

Tarceva monotherapy

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

The most frequent ADRs were rash and diarrhoea (any Grade 75% and 54% respectively), most were Grade 1/2 in severity and manageable without intervention. Grade 3 or Grade 4 rash and diarrhoea occurred in 9% and 6%, respectively in patients treated with Tarceva and each resulted in study discontinuation in 1% of patients. Dose reduction for rash and diarrhoea was needed in 6% and 1% of patients, respectively. In study BR.21 the median time to onset of rash was 8 days and the median time to onset of diarrhoea was 12 days.

Table 1: ADRs occurring more frequently ($\geq 3\%$) in the Tarceva group than in the placebo group and in $\geq 10\%$ of patients in the Tarceva group in Study BR.21

NCI-CTC Grade	Erlotinib <i>n</i> = 485			Placebo <i>n</i> = 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
<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.

In another double-blind, randomised, placebo-controlled Phase III study (BO18192) 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 or Grade 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.

Tarceva in combination with chemotherapy

The ADRs listed in Table 2 below are based on erlotinib-arm data from a controlled clinical trial (PA.3), 259 patients with pancreatic cancer received Tarceva 100 mg plus gemcitabine compared to 256 patients in the placebo plus gemcitabine-arm.

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

patients, and resulted in study discontinuation in up to 1% of patients receiving Tarceva plus gemcitabine.

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

Table 2: ADRs occurring $\geq 10\%$ and more frequently ($\geq 3\%$) in Tarceva 100 mg plus gemcitabine-treated patients than in the placebo plus gemcitabine group in Study PA.3

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.*

Further information on adverse reactions of special interest

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

The following terms are used to rank the adverse reactions by frequency: very common ($\geq 1/10$); common ($\geq 1/100 < 1/10$); uncommon ($\geq 1/1000 < 1/100$); rare ($\geq 1/10,000 < 1/1000$); very rare ($< 1/10,000$) including isolated reports.

Very common ADRs are presented in Tables 1 and 2, ADRs in other frequency categories are summarised below.

Gastrointestinal disorders

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

Cases of gastrointestinal bleeding have been reported commonly (including some fatalities), some associated with concomitant warfarin administration (See Interactions with other Medicinal Products and other Forms of Interaction) and some with concomitant NSAIDs.

Hepatobiliary disorders

Liver function test abnormalities (including raised alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin) have been observed commonly in clinical trials of Tarceva. In study PA.3, these occurred very commonly. They were mainly mild or moderate in severity, transient in nature or associated with liver metastases. Rare cases of hepatic failure (including fatalities) have been reported during use of Tarceva. Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medications (see Warnings and Precautions).

Eye disorders

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

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

Respiratory, thoracic and mediastinal disorders

There have been uncommon reports of serious interstitial lung disease (ILD)-like events (including fatalities) in patients receiving Tarceva for treatment of NSCLC and other advanced solid tumours (see Warnings and Precautions).

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

Skin and subcutaneous tissue disorders

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

Bullous, blistering and exfoliative skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal (see Warnings and Precautions).

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

Post Marketing Experience

Skin and subcutaneous tissue disorders:

Hair and nail changes, mostly non-serious, have been reported uncommonly from post-marketing surveillance, e.g. hirsutism, eyelash/eyebrow changes, paronychia and brittle and loose nails.

Overdose

Single oral doses of Tarceva up to 1000 mg in healthy subjects and up to 1600 mg given as a single dose once weekly in cancer patients have been tolerated. Repeated twice daily doses of 200 mg in healthy subjects were poorly tolerated after only a few days of dosing. Based on the data from these studies, severe adverse events such as diarrhoea, rash and possibly liver transaminase elevation may occur above the recommended dose. In case of suspected overdose Tarceva should be withheld and symptomatic treatment administered.

Pharmacological Properties & Effects

Pharmacodynamic Properties

Mechanism of action

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

Clinical/efficacy studies

Non-Small Cell Lung Cancer (NSCLC) (Tarceva administered as monotherapy)

First line maintenance therapy

The efficacy and safety of Tarceva as first-line maintenance therapy of NSCLC was demonstrated in a randomised, double-blind, placebo-controlled trial (BO18192). This study was conducted in 889 patients with locally advanced or metastatic NSCLC who did not progress during 4 cycles of platinum-based doublet chemotherapy. Patients were randomised 1:1 to receive Tarceva 150 mg or placebo

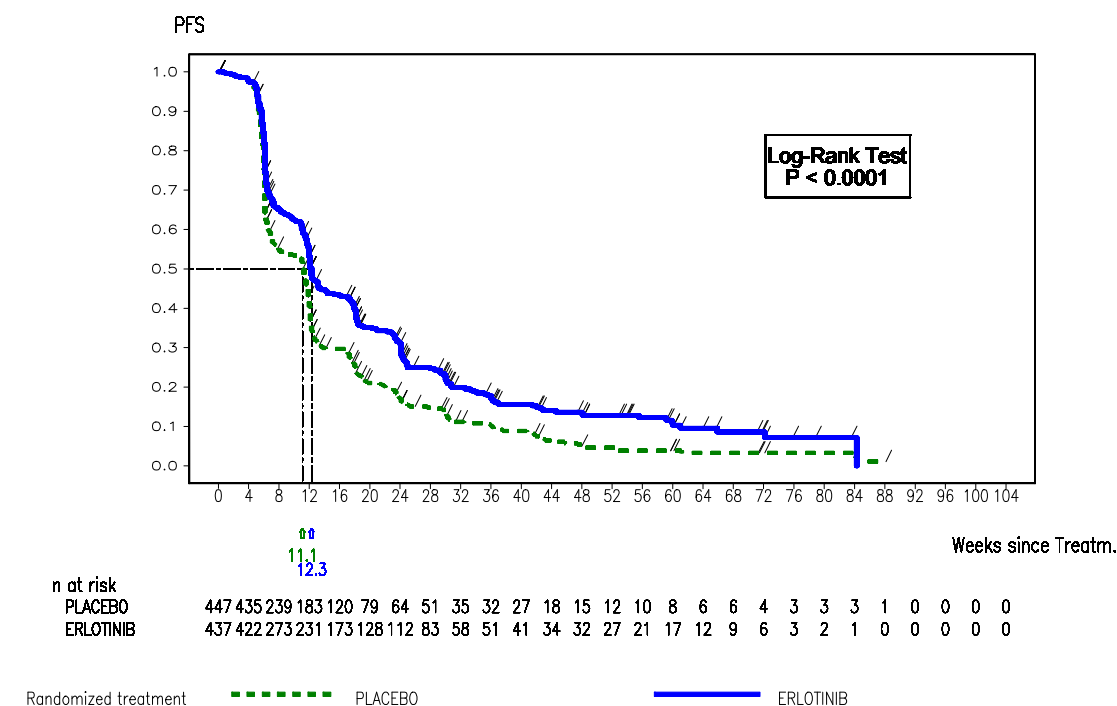
orally once daily. The primary end-point of the study was progression free survival (PFS) in all patients and in patients with an EGFR IHC positive tumour. Baseline demographic and disease characteristics were well balanced between the two treatment arms.

Table 3 shows the results of the primary PFS analysis in the intent-to-treat (ITT) population. The primary PFS analysis in all patients showed a hazard ratio for PFS in the Tarceva group relative to the placebo group of 0.71. The mean PFS was 22.4 weeks in the Tarceva group compared with 16.0 weeks in the placebo group.

Table 3: Study BO18192 Efficacy Results (ITT population)

	Tarceva 150 mg (n = 438)	Placebo (n = 451)	p-value
Hazard ratio	0.71		$p < 0.0001$
(95% CI)	(0.62 to 0.82)		
Median PFS	12.3 weeks	11.1 weeks	
Mean PFS	22.4 weeks	16.0 weeks	
(range)	(0.1 to 84.3 weeks)	(0.1 to 88.1 weeks)	
6 months PFS rate	25%	15%	
Disease Control Rate (CR, PR, SD > 12 weeks)	40.8%	27.4%	$p < 0.0001$

Figure 1: Kaplan-Meier Curve for PFS of Patients by Treatment Group in Study BO18192



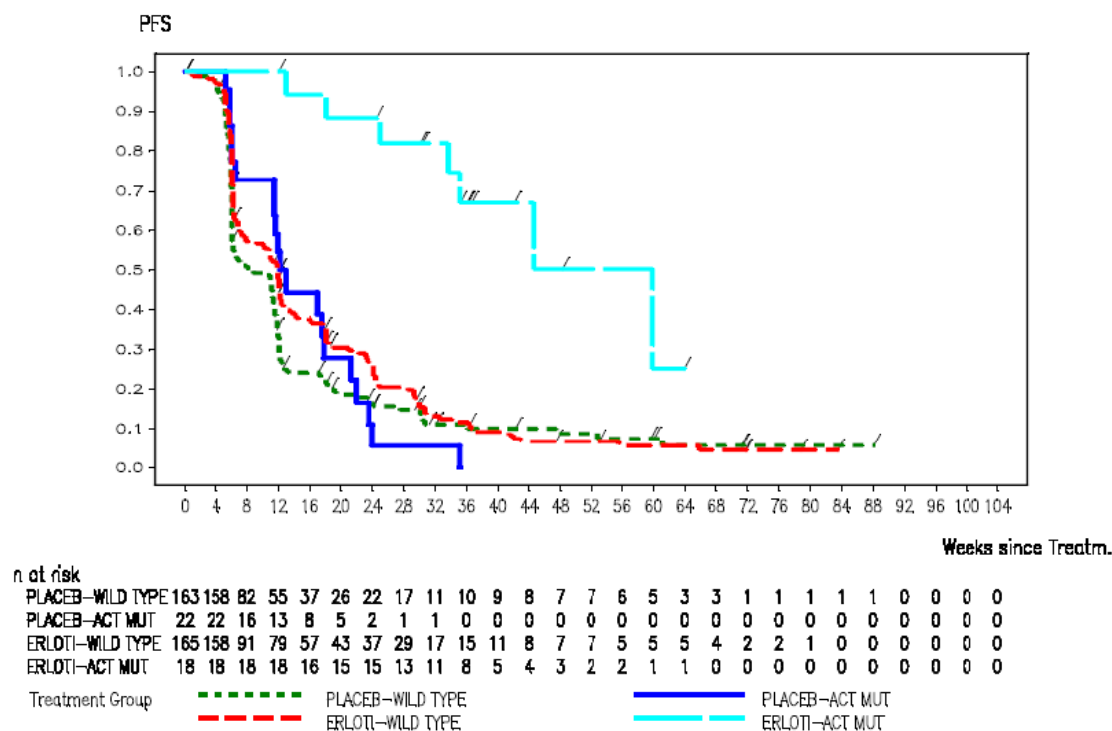
Cut-off for statistical analysis: 17MAY2008
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The co-primary PFS analysis in patients with an EGFR IHC positive tumour was similar, with a hazard ratio of 0.69 (95% CI, 0.58 to 0.82) ($p < 0.0001$). The mean PFS was 22.8 weeks in the Tarceva group (range 0.1 to 78.9 weeks) compared with 16.2 weeks in the placebo group (range 0.1 to 88.1

weeks). The percentages of patients without progression at 6 months were 27% and 16%, respectively.

The efficacy was shown to be consistent across subgroups based on stratification and clinical factors. Benefit was also observed across biomarker subgroups independent of EGFR IHC, FISH, EGFR mutation or K-ras mutation status. Activating EGFR mutations have identified patients with the largest benefit (HR = 0.10; $p < 0.0001$) (Figure 2).

Figure 2: Kaplan-Meier Curve of PFS by Study Treatment and EGFR Mutation Status (Activating Mutation and Wild Type)



Quality of life did not suggest a detrimental effect from erlotinib compared with placebo.

The benefit in PFS translated into statistically significant and clinically relevant benefit in overall survival (secondary end-point, HR = 0.81, see Table 4).

Table 4: Study BO18192 Efficacy Results, Overall Survival (ITT population)

	Tarceva 150 mg (n = 438)	Placebo (n = 451)	p-value
Hazard ratio	0.81		p = 0.0088
(95% CI)	(0.70 to 0.95)		
Median Overall Survival	12.0 months	11.0 months	

In the EGFR IHC positive population the median OS was 11.0 months in the placebo group and 12.8 months in the Tarceva group (HR 0.77; 95% CI: 0.64 – 0.93; $p = 0.0063$).

Second or third line therapy

The efficacy and safety of Tarceva in second or third line therapy of NSCLC was demonstrated in a randomised, double-blind, placebo-controlled trial (BR.21). This study was conducted in 17 countries, in 731 patients with locally advanced or metastatic NSCLC after failure of at least one chemotherapy regimen. Patients were randomised 2:1 to receive Tarceva 150 mg or placebo orally once daily. Study end points included overall survival, time to deterioration of lung cancer-related symptoms (cough, dyspnoea and pain), response rate, duration of response, progression-free survival (PFS) and safety. The primary end-point was survival.

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

Demographic characteristics were well balanced between the two treatment arms. About two-thirds of the patients were male and approximately one-third had a baseline ECOG performance status (PS) of 2 and 9% had a baseline ECOG of 3. Ninety-three percent and 92% of all patients in the Tarceva and placebo groups, respectively, had received a prior platinum-containing regimen and 36% and 37% of all patients, respectively, had received a prior taxane therapy. Fifty percent of the patients had received only one prior regimen of chemotherapy.

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

The survival benefit with Tarceva treatment was seen across most subsets. A series of subsets of patients formed by the values of the stratification factors at randomisation and at baseline, HER1/EGFR status, prior exposure to taxanes, smoking history, gender, age, histology, prior weight loss, time between initial diagnosis and randomisation and geographic location were examined in exploratory univariate analyses to assess the robustness of the overall survival result. Nearly all of the hazard ratios (HR) in the Tarceva group relative to the placebo group were less than 1.0, suggesting that the survival benefit from Tarceva was robust across subsets. Of note, the survival benefit of Tarceva was comparable in patients with a baseline ECOG PS of 2-3 (HR = 0.77) or a PS of 0-1 (HR = 0.73) and patients who had received one chemotherapy regimen (HR = 0.76) or two or more regimens (HR = 0.76).

A survival benefit of Tarceva was also observed in patients who did not achieve an objective tumour response (by RECIST). This was evidenced by a HR for death of 0.83 among patients whose best response was stable disease and 0.85 among patients whose best response was progressive disease.

Table 5 summarises the results for the study, including survival, time to deterioration of lung cancer-related symptoms and progression free survival (PFS).

Table 5: Study BR.21 Efficacy Results

	Tarceva (n = 488)	Placebo (n = 243)	p-value
Median Survival 95 % CI	6.7 months (5.5 to 7.8)	4.7 months (4.1 to 6.3)	
Difference between Survival Curves			0.001
Hazard Ratio*, Mortality (Erlotinib: Placebo) 95 % CI (Risk Ratio)	0.73 0.60 to 0.87		
Median Time to Deterioration in Cough*** 95 % CI	28.1 weeks (16.1 to 40.0)	15.7 weeks (9.3 to 24.3)	0.041
Median Time to Deterioration in Dyspnoea*** 95 % CI	20.4 weeks (16.3 to 28.3)	12.1 weeks (9.3 to 20.9)	0.031**
Median Time to Deterioration in Pain*** 95 % CI	12.1 weeks (10.1 to 14.1)	8.1 weeks (7.7 to 12.3)	0.040**
Median Progression-free Survival 95 % CI	9.7 weeks (8.4 to 12.4)	8.0 weeks (7.9 to 8.0)	<0.001

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

** p-value adjusted for multiple testing

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

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

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

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

Pancreatic cancer (Tarceva administered concurrently with gemcitabine)

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

gemcitabine plus placebo (260 patients in the 100 mg cohort and 24 patients in the 150 mg cohort). Too few observations were made for the 150 mg cohort to draw conclusions.

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

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

Table 6 summarises the results of the study.

Table 6: Study PA.3 Efficacy Results

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

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

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

Pharmacokinetic Properties

Exposure

Following a 150 mg oral dose of Tarceva, at steady state, the median time to reach maximum plasma concentrations is approximately 4 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 41.3 mcg*h/mL.

Absorption

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

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

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 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% 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. Tissue distribution studies using whole body autoradiography following oral administration with [¹⁴C] labelled erlotinib in athymic nude mice with HN5 tumour xenografts have shown rapid and extensive tissue distribution with maximum concentrations of radiolabelled erlotinib (approximately 73% of that in plasma) observed at 1 hour.

Metabolism

Erlotinib is metabolised in humans by hepatic cytochrome P450 enzymes, primarily by CYP3A4 and to a lesser extent by CYP1A2. Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung and CYP1B1 in tumour tissue potentially contribute to the metabolic clearance of erlotinib. *In vitro* studies indicate approximately 80 - 95% of erlotinib metabolism is by the CYP3A4 enzyme. There are three main metabolic pathways identified: 1) O-demethylation of either side chain or both, followed by oxidation to the carboxylic acids; 2) oxidation of the acetylene moiety followed by hydrolysis to the aryl carboxylic acid; and 3) aromatic hydroxylation of the phenyl-acetylene moiety. The primary metabolites of erlotinib produced by O-demethylation of either side chain have comparable potency to erlotinib in preclinical *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

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

Clearance

A population pharmacokinetic analysis in 591 patients receiving single agent Tarceva showed 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. Elevated serum concentrations of total bilirubin and AAG were associated with a slower rate of erlotinib clearance. Smokers had a higher rate of erlotinib clearance (see Interactions with other Medicinal Products and other Forms of Interaction).

A second population pharmacokinetic analysis was conducted to incorporate 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 non-smoking subjects and healthy subjects who currently smoke has shown that cigarette smoking leads to increased clearance of, and decreased exposure to, erlotinib. The $AUC_{0-\infty}$ in smokers was about 1/3 of that in never/former smokers ($n = 16$ in each of the smoker and never/former smoker arms). This reduced exposure in smokers is presumably due to induction of CYP1A1 in the lungs and CYP1A2 in the liver.

In the pivotal Phase III NSCLC trial, smokers achieved an erlotinib steady state trough plasma concentration of 0.65 mcg/mL ($n = 16$) which was approximately 2-fold less than the former smokers or patients who had never smoked (1.28 mcg/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 smokers in this study was 1.22 mcg/mL ($n = 17$) (see Special Dosage Instructions, Interactions with other Medicinal Products and other Forms of Interaction).

Preclinical Safety

Carcinogenicity

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

Mutagenicity

Erlotinib was negative in the standard battery of genotoxicity assays.

Impairment of fertility

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

Teratogenicity

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

Other

Chronic dosing effects observed in at least 1 animal species or study included effects on the cornea (atrophy, ulceration), skin (follicular degeneration and inflammation, redness and alopecia), ovary (atrophy), liver (liver necrosis), kidney (renal papillary necrosis and tubular dilatation) and gastrointestinal tract (delayed gastric emptying and diarrhoea). Red blood cell (RBC) counts, haematocrit and haemoglobin were decreased and reticulocytes were increased. White blood cells (WBCs), primarily neutrophils, were increased. There were treatment-related increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin.

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

Pharmaceutical Particulars

Stability

Store below 30°C.

Tarceva film-coated tablets should be stored in the original container.

This medicine should not be used after the expiry date shown on the pack.

Disposal

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

Packs

Tarceva 25 mg, 100 mg and 150 mg film-coated tablets are available in blister packs containing 30 tablets.



Medicine Classification

Prescription Medicine

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