AUSTRALIAN PRODUCT INFORMATION
Tarceva® (Erlotinib hydrochloride)

1. NAME OF THE MEDICINE
Erlotinib hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Tarceva film coated tablets are available in 3 dosage strengths containing erlotinib hydrochloride equivalent to 25 mg, 100 mg or 150 mg of erlotinib.

Excipients with known effect
Each 25 mg film-coated tablet contains 27.43 mg Lactose monohydrate.

Each 100 mg film-coated tablet contains 69.21 mg Lactose monohydrate.

Each 150 mg film-coated tablet contains 103.82 mg Lactose monohydrate.

For the full list of excipients, see section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM
Tarceva 25 mg film-coated tablets are white to yellowish, round, biconvex tablets engraved with 'T 25' on one side.

Tarceva 100 mg film-coated tablets are white to yellowish, round, biconvex tablets engraved with 'T 100' on one side.

Tarceva 150 mg film-coated tablets are white to yellowish, round, biconvex tablets engraved with 'T 150' on one side.

4. CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Non-small cell lung cancer
Tarceva is indicated for the first-line treatment of patients with advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer (NSCLC) with activating EGFR mutations.

Tarceva is indicated for maintenance therapy in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutations who have not progressed on 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 prior chemotherapy.

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

4.2 DOSE AND METHOD OF ADMINISTRATION
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. Treatment should be continued until disease progression or

unacceptable toxicity occurs. There is no evidence that treatment beyond disease progression is beneficial.

When 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 the gemcitabine Product Information for the correct dosage of gemcitabine in pancreatic cancer). Treatment should be continued until disease progression or unacceptable toxicity occurs.

Special Dosage Instructions
Concomitant use of CYP3A4 substrates and modulators may require dose adjustment (see sections 4.4 Special warnings and precautions for use and 4.5 Interactions with other medicines and other forms of interactions).

Hepatic impairment
Tarceva treatment should be interrupted or discontinued if;

- there is a doubling of total serum bilirubin and/or tripling of serum transaminases in patients with baseline hepatic impairment
- total serum bilirubin is > 3 x ULN and/or serum transaminases are > 5 x ULN in patients with normal pre-treatment values. (See section 4.4 Special warnings and precautions for use)

Paediatric Populations
The safety and efficacy of Tarceva has not been studied in patients under the age of 18 years.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
EGFR Mutation Status
It is recommended that EGFR mutation testing should be performed prior to initiation of Tarceva as first-line or maintenance therapy in patients with locally advanced or metastatic NSCLC. A well-validated and robust test for activating EGFR mutations should be used.

Combination with Chemotherapy
Randomised controlled trials have demonstrated that Tarceva combined with doublet, platinum-based cytotoxic chemotherapy in advanced NSCLC provides no added benefit over cytotoxic chemotherapy alone.

Interstitial Lung Disease (ILD)
Cases of ILD-like events, including fatalities, have been reported uncommonly in patients receiving Tarceva for treatment of NSCLC, pancreatic cancer or other advanced solid tumours. In the pivotal Phase III study BR.21 in NSCLC, the incidence of serious ILD-like events (0.8%) was the same in both the placebo and Tarceva groups. In a meta-analysis of NSCLC randomised controlled clinical trials, the incidence of ILD-like events was 0.9% on Tarceva compared to 0.4% in patients in the control arms.

In the pancreatic cancer study in combination with gemcitabine, the incidence of ILD-like events was 2.5% in the Tarceva plus gemcitabine group versus 0.4% in the placebo plus

gemcitabine-treated group. Some examples of reported diagnoses in patients suspected of having ILD-like events included 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. A causal association of ILD-like events to Tarceva therapy has not been established.

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 section 4.8 Adverse effects (Undesirable effects)).

ECG Effects

In vitro studies indicate that Tarceva blocks the hERG K^+ channel, producing 20% inhibition at concentrations 1.6 – 8 times higher than the peak free Tarceva concentration in humans and therefore has the potential to inhibit cardiac action potential repolarisation. The clinical significance of these findings is unknown and adverse ECG effects have not been observed in human studies to date.

Diarrhoea and Dehydration

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.

Hypokalaemia, Renal Failure

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.

Lactose Intolerance

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

Hepatotoxicity, Hepatitis, Hepatic Failure

Liver function test abnormalities (including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin) have been observed infrequently. These were mainly mild or moderate in severity, transient in nature or associated with liver metastases.

Rare cases of hepatic failure and hepatorenal syndrome (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 treatment should be interrupted or discontinued if changes in liver function are severe (see sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use).

Gastrointestinal Perforations
Patients receiving Tarceva are at an increased risk of developing gastrointestinal perforation, which was observed uncommonly (including some cases with a fatal outcome). Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at increased risk. Tarceva should be permanently discontinued in patients who develop gastrointestinal perforation (see section 4.8 Adverse effects (Undesirable effects)).

Bullous and Exfoliative Skin Disorders
Bullous, blistering and exfoliative skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal (see section 4.8 Adverse effects (Undesirable effects)). Tarceva treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliative 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 section 4.8 Adverse effects (Undesirable effects)).

Use in the elderly
Of the total number of patients participating in the Phase III study BR. 21, 62% were less than 65 years of age and 38% of patients were aged 65 years or older. The survival benefit was maintained across both age groups (see section 5.1 Pharmacodynamic properties). No meaningful differences in safety or pharmacokinetics were observed between younger and older patients. Therefore, no dosage adjustments are recommended in elderly patients.

Use in renal impairment
The safety and efficacy of Tarceva has not been studied in patients with renal impairment.

Use in hepatic impairment
In view of the variability in pharmacokinetics, Tarceva should be used with caution in patients with hepatic impairment and the dose tailored to individual patients (see section 5.2 Pharmacokinetics in Special Populations, Hepatic Impairment).

Patients with hepatic impairment are at increased risk of hepatic failure during treatment with Tarceva. Therefore, close monitoring of hepatic function is recommended. Tarceva treatment should be interrupted or discontinued if changes in hepatic function are severe (see sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use).

The safety and efficacy of Tarceva have not been studied in patients with severe hepatic impairment (total serum bilirubin > 3 x ULN). Use of Tarceva in patients with severe hepatic impairment is not recommended.

Paediatric Use
The safety and efficacy of Tarceva has not been studied in patients under the age of 18 years.

Effects on laboratory tests
No data available

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Tarceva is metabolised by the hepatic cytochromes in humans, primarily CYP3A4/CYP3A5 and to a lesser extent by CYP1A2 and the pulmonary isoform CYP1A1. Potential interactions may occur with medicines that are metabolised by, or are inhibitors or inducers of, these enzymes.

Potent inhibitors of CYP3A4 activity decrease erlotinib metabolism and increase erlotinib plasma concentrations. Inhibition of CYP3A4 metabolism by ketoconazole (200 mg orally twice daily for 5 days) resulted in increased exposure to Tarceva (86% in median Tarceva AUC) and a 69% increase in maximum concentration (C_{max}) when compared to Tarceva alone. When Tarceva was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2, Tarceva 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 such as ketoconazole, atazanavir, clarithromycin, erythromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin and voriconazole. In these situations, the dose of Tarceva should be reduced if toxicity is observed.

Potent inducers of CYP3A4 increase erlotinib metabolism and significantly decrease erlotinib plasma concentrations. Induction of CYP3A4 metabolism by rifampicin (600 mg orally, 4 times a day for 7 days) resulted in a 69% decrease in the median Tarceva AUC, following a 150 mg dose of Tarceva, as compared to Tarceva alone.

In another study, 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. Therefore, caution should be used when administering Tarceva with potent CYP3A4 inducers such as rifampicin, rifabutin, rifapentin, phenytoin, carbamazepine, phenobarbital and St. John's Wort. 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 did appear to decrease by up to 24%, which was however not attributed to effects on CYP3A4 activity.

The solubility of Tarceva is pH dependent. Tarceva solubility decreases as pH increases. Medicines that alter the pH of the upper gastrointestinal tract may alter the solubility of Tarceva and hence its bioavailability. Co-administration of Tarceva with omeprazole, a proton pump inhibitor, decreased the Tarceva exposure [AUC] and C_{max} by 46% and 61% respectively. There was no change to T_{max} or half-life. Concomitant administration of Tarceva with 300 mg ranitidine, a H_2-receptor antagonist, decreased Tarceva exposure [AUC] and C_{max} by 33% and 54% respectively. Therefore, co-administration of Tarceva with medicines that reduce gastric acid production should be avoided where possible. Increasing the dose of Tarceva is not likely to compensate for loss of exposure. However, when Tarceva was dosed in a staggered manner 2 hours before or 10 hours after ranitidine 150 mg twice daily, Tarceva exposure [AUC] and C_{max} decreased by 15% and 17% respectively. If patients need to be treated with such medicines, 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.

International Normalized Ratio (INR) elevations and bleeding events, including gastrointestinal bleeding, have been reported in clinical studies, some associated with concomitant warfarin administration. Patients taking warfarin or other coumarin-derivative anticoagulants 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.

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

The impact of smoking on Tarceva efficacy is not known, however, smokers should be advised to stop smoking as cigarette smoking, which is known to induce CYP1A1 and CYP1A2, has been shown to reduce Tarceva exposure by 50 – 60% (see section 5.2 Pharmacokinetic properties).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Tarceva did not impair fertility in male rats given doses that result in plasma drug concentrations similar to that of humans. Tarceva administered at 10 mg/kg/day (1.5 times the clinical dose based on relative AUC) for 2 weeks prior to mating until day 7 of gestation affected ovulation in female rats, resulting in a reduction in the number of corpora lutea.

Use in Pregnancy – Category C

There are no adequate or well-controlled studies in pregnant women using Tarceva. Studies in animals have shown some reproductive toxicity (see section 5.3 Preclinical safety data). The potential 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.

Use in Lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Safety evaluation of Tarceva is based on the data from more than 1500 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 reactions 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 adverse reactions were those reported in at least 10% (in the Tarceva group) of patients and occurred more frequently (≥ 3%) in patients treated with Tarceva than in the comparator arm.

Tarceva Monotherapy

The adverse reactions listed in Table 1 are based on data from the pivotal 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, taken orally once daily until disease progression or unacceptable toxicity.

The most frequent adverse reactions 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 Tarceva-treated patients and each resulted in study discontinuation in 1% of patients. Rash and diarrhoea diminished following discontinuation of Tarceva. 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: Adverse reactions occurring more frequently (≥ 3%) in Tarceva-treated group than in the placebo group and in ≥ 10% of patients in the Tarceva group in study BR.21

	Tarceva *n* = 485			**Placebo *n* = 242**		
NCI-CTC Grade	**Any Grade**	**3**	**4**	**Any Grade**	**3**	**4**
MedDRA Preferred Term	**%**	**%**	**%**	**%**	**%**	**%**
Total patients with any AE	99	40	22	96	36	22
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

	Tarceva *n* = 485			Placebo *n* = 242		
NCI-CTC Grade	**Any Grade**	**3**	**4**	**Any Grade**	**3**	**4**
MedDRA Preferred Term	**%**	**%**	**%**	**%**	**%**	**%**
Total patients with any AE	99	40	22	96	36	22
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
General disorders and administration site conditions						
Fatigue	52	14	4	45	16	4
Metabolism and nutrition disorders						
Anorexia	52	8	1	38	5	<1
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	41	17	11	35	15	11
Cough	33	4	0	29	2	0
*Infections and infestations**						
Infection	24	4	0	15	2	0
Eye disorders						
Conjunctivitis	12	<1	0	2	<1	0
Keratoconjunctivitis sicca	12	0	0	3	0	0

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

In two other double-blind, randomised, placebo-controlled Phase III studies (BO18192 and BO25460) conducted in a total of 1532 patients with advanced, recurrent or metastatic NSCLC following first-line standard platinum-based chemotherapy, no new safety signals were identified in the safety analysis population.

The most frequent adverse reaction seen in patients treated with Tarceva in studies BO18192 and BO25460 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 BO18192, while no patient discontinued for rash or diarrhoea in BO25460. Dose modifications (interruptions or reductions) for rash and diarrhoea were needed in 8.3% and 3% of patients, respectively, in Study BO18192 and 5.6% and 2.8% of patients, respectively, in Study BO25460.

Table 2: ADR table for the most frequent ADRs in BO18192 (SATURN) and BO25460 (IUNO) Studies

	BO18192 (SATURN)*		BO25460 (IUNO)*	
MedDRA 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 the open-label, randomised phase III study ML 20650, conducted in 154 patients, the safety of Tarceva for first-line treatment of NSCLC patients with EGFR activating mutations was assessed in 75 patients; no new safety signals were observed in these patients.

The most frequent adverse reactions seen in patients treated with Tarceva in study ML 20650 were rash and diarrhoea (any Grade 80% and 57%, respectively), most were Grade 1 - 2 in severity and manageable without intervention. Grade 3 rash and diarrhoea occurred in 9% and 4% of patients, respectively. No Grade 4 rash or diarrhoea was observed. Both rash and diarrhoea resulted in discontinuation of Tarceva in 1% of patients. Dose modifications (interruptions or reductions) for rash and diarrhoea were needed in 11% and 7% of patients, respectively.

Tarceva in Combination with Chemotherapy

The adverse reactions listed in Table 3 are based on the Tarceva arm data from a 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 frequent adverse reactions in study PA.3 in pancreatic cancer patients receiving Tarceva 100 mg plus gemcitabine were fatigue (73%), rash (69%) and diarrhoea (48%). In the Tarceva plus gemcitabine arm, Grade 3 or Grade 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 3: Adverse reactions occurring ≥ 10% and more frequently (≥ 3%) in Tarceva 100 mg plus gemcitabine-treated patients than in the placebo plus gemcitabine group in Study PA.3

	Tarceva plus gemcitabine *n* = 259			**Placebo plus gemcitabine *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
Skin and subcutaneous tissue disorders						
Rash	69	5	0	30	1	0
Alopecia	14	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
Metabolism and nutrition disorders						
Weight decreased	39	2	0	29	<1	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
Infections and infestations						
Infection*	31	3	<1	24	6	<1
Psychiatric disorders						
Depression	19	2	0	14	<1	0
Respiratory, thoracic and mediastinal disorders						
Cough	16	0	0	11	0	0
Nervous system disorders						
Headache	15	<1	0	10	0	0
Neuropathy	13	1	<1	10	<1	0

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

Further Information on Adverse Reactions of Special Interest:

The following adverse reactions have been observed in patients who received Tarceva monotherapy or Tarceva 100 mg and 150 mg in combination with gemcitabine.

The following terms are used to rank the adverse reactions 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.

Very common adverse reactions are presented in Tables 1, 2 and 3, adverse events 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 section 4.4 Special warnings and precautions for use). Cases of gastrointestinal bleeding have been reported commonly (including some fatalities), some associated with concomitant warfarin administration (see sections 4.4 Special warnings and precautions for use and 4.5) and some with concomitant NSAID administration.

Hepatobiliary disorders
Liver function test abnormalities (including elevated 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 and hepatorenal syndrome (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 Special warnings and precautions for use).

Eye disorders
Corneal ulcerations or perforations have been reported very rarely in patients receiving Tarceva treatment (see section 4.4 Special warnings and precautions for use).

Keratitis and conjunctivitis has been reported commonly with Tarceva. Abnormal eyelash growth including: in-growing eyelashes, excessive growth and thickening of the eyelashes have been reported (see section 4.4 Special warnings and precautions for use).

Respiratory, thoracic and mediastinal disorders
There have been uncommon reports of serious interstitial lung disease, including fatalities, in patients receiving Tarceva for treatment of NSCLC and other advanced solid tumours.

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

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

Bullous, blistering and exfoliative skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal (see section 4.4 Special warnings and precautions for use). 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.

Cardiovascular disorders
In the pivotal pancreatic cancer trial there was an excess of myocardial infarction/ischaemia (2.3% vs 1.2%) and cerebrovascular accidents (2.3% vs 0%) in the Tarceva/gemcitabine group compared to the placebo/gemcitabine group.

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.

Cases of uveitis have been reported during post-marketing surveillance.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 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 of 150 mg. In case of suspected overdose, Tarceva should be withheld and symptomatic treatment initiated. Treatment should consist of general supportive measures.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: antineoplastic agent protein kinase inhibitor, ATC code: L01EB02

Mechanism of Action
Erlotinib potently inhibits the intracellular phosphorylation of HER1/EGFR tyrosine kinase with nanomolar potency; HER1/EGFR is expressed on the cell surface of normal cells and cancer cells of epithelial origin. However, the mechanism of antitumour action of erlotinib is not fully characterised. Erlotinib has been demonstrated to inhibit proliferation and/or induce apoptosis in human cancer cell lines *in vitro* and to inhibit the growth of a variety of human tumour xenografts in nude mice. Specificity of inhibition with regard to other tyrosine kinase receptors has not been fully characterised.

Clinical trials
Non-Small Cell Lung Cancer (NSCLC) – Tarceva Monotherapy
First-line therapy for patients with Epidermal Growth Factor Receptor (EGFR) activating mutations

The efficacy of Tarceva in first-line treatment of patients with EGFR activating mutations in NSCLC was demonstrated in a phase III, randomised, open-label trial (ML20650, EURTAC). This study was conducted in Caucasian patients with metastatic or locally advanced NSCLC (stage IIIB and IV) who have not received previous chemotherapy or any systemic antitumour therapy for their advanced disease and who present mutations in the tyrosine kinase domain of the EGFR (exon 19 deletion or exon 21 mutation). Patients were randomised 1:1 to receive Tarceva 150 mg orally once daily or platinum based doublet chemotherapy.

The primary endpoint of investigator assessed progression free survival (PFS), was determined at a pre-planned interim analysis (n=153, hazard ratio (HR) = 0.42, 95 % CI, 0.27 to 0.64; p<0.0001 for the Tarceva group (n=77) relative to the chemotherapy group (n=76)). A 58% reduction in the risk of disease progression or death was observed. In the Tarceva versus chemotherapy arms, median PFS was 9.4 and 5.2 months, respectively. The median duration of follow-up was 14.3 months for erlotinib patients and 10.7 months for chemotherapy patients. Objective response rate (ORR) was 54.5 % and 10.5%, respectively. PFS results were confirmed by an independent review of the scans, median PFS was 10.4 months in the Tarceva group compared with 5.4 months in the chemotherapy group (HR=0.47, 95 % CI, 0.28 to 0.78; p=0.003). The overall survival (OS) data were immature at the time of interim analysis (HR= 0.80, 95 % CI, 0.47 to 1.37, p=0.4170).

At an updated analysis with 62% of OS maturity, OS HR was 0.93 (95% CI, 0.64 to 1.36, p = 0.7149). A high crossover was observed with 82% of the patients in the chemotherapy arm receiving subsequent therapy with an EGFR tyrosine kinase inhibitor and all but 2 of those patients had subsequent Tarceva. In the updated analysis, PFS results remained consistent with the interim analysis results. Median PFS assessed by the investigators was 10.4 and 5.1 months in the Tarceva and chemotherapy arms respectively (HR = 0.34, 95% CI, 0.23 to 0.49, p<0.0001).

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 (SATURN). This study was conducted in 889 patients with locally advanced or metastatic NSCLC who did not progress during 4 cycles of platinum-based doublet chemotherapy. Patients were randomised 1:1 to receive Tarceva 150 mg or placebo orally once daily. The co-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.

In this study BO18192 (SATURN), the overall population showed a benefit for the primary PFS end-point (HR= 0.71 p<0.0001) and the secondary OS end-point (HR=0.81 p=0.0088). However the largest benefit was observed in a predefined exploratory analysis in patients with EGFR activating mutations (n=49) demonstrating a substantial PFS benefit (HR=0.10, 95% CI, 0.04 to 0.25; p<0.0001) and an overall survival HR of 0.83 (95% CI, 0.34 to 2.02; p<0. 6810). 67% of placebo patients in the EGFR mutation positive subgroup received second or further line treatment with EGFR-TKIs. In patients with EGFR wild type 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). The study was not powered to show statistically significant differences for OS in the EGFR wild type and EGFR mutation positive subgroups.

The BO25460 (IUNO) study was conducted in 643 patients with advanced NSCLC whose tumours did not harbour an EGFR-activating mutation (exon 19 deletion or exon 21 L858R

mutation) and who had not experienced disease progression after four cycles of platinum-based chemotherapy.

The objective of the study was to compare the overall survival of first line maintenance therapy with erlotinib versus erlotinib administered at the time of disease progression. The study did not meet its primary endpoint. OS of Tarceva in first line maintenance was not superior to Tarceva as second line treatment in patients whose tumour did not harbour an EGFR-activating mutation (HR=1.02, 95% CI, 0.85 to 1.22, p=0.82). The secondary endpoint of PFS showed no difference between Tarceva and placebo in maintenance treatment (HR=0.94, 95% CI, 0.80 to 1.11; p=0.48).

Based on the data from the BO25460 (IUNO) study, Tarceva use is not recommended for first-line maintenance treatment in patients without an EGFR activating mutation.

Second-line and third-line therapy
The efficacy and safety of Tarceva in second and third line therapy of NSCLC was demonstrated in a randomised, double-blind, placebo-controlled trial (Study 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, following disease progression, were randomised 2:1 to receive Tarceva 150 mg (*n* = 488) or placebo (*n* = 243) orally once daily. Study endpoints included overall survival, time to deterioration of lung cancer-related symptoms (cough, dyspnoea and pain), response rate, duration of response, progression-free survival (PFS) and safety. The primary end-point was survival.

Patients were not selected for HER1/EGFR status, gender, race, smoking history or histologic classification. Demographic characteristics were well balanced between the two treatment groups (see Table 4). Approximately 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. Fifty percent of the patients had received only one prior regimen of chemotherapy.

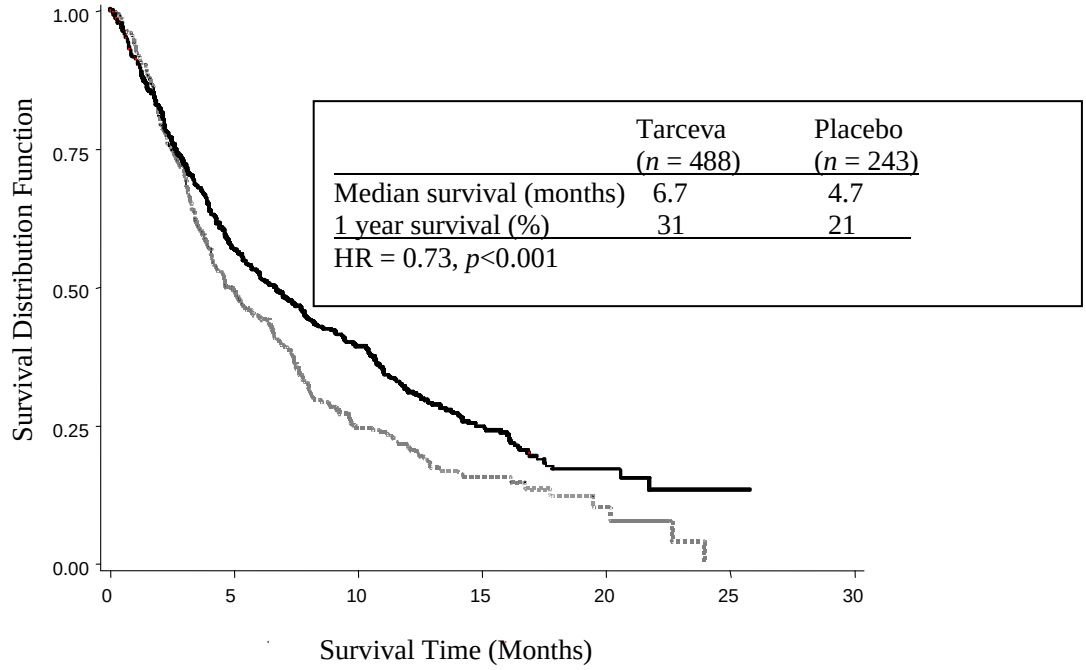
Table 4: Study BR.21- Demographic and Disease Characteristics

Characteristics	Tarceva *n* = 488		Placebo *n* = 243	
	n	**(%)**	***n***	**(%)**
Gender				
Female	173	(35)	83	(34)
Male	315	(65)	160	(66)
Age (years)				
< 65	299	(61)	153	(63)
≥ 65	189	(39)	90	(37)
ECOG Performance Status				
0	64	(13)	34	(14)
1	256	(52)	132	(54)
2	126	(26)	56	(23)
3	42	(9)	21	(9)
Smoking History				
Never smoked	104	(21)	42	(17)
Current or Ex-smoker	358	(73)	187	(77)

Characteristics	Tarceva *n* = 488		Placebo *n* = 243	
	n	**(%)**	***n***	**(%)**
Unknown	26	(5)	14	(6)
Histological Classification				
Adenocarcinoma	246	(50)	119	(49)
Squamous	144	(30)	78	(32)
Undifferentiated Large Cell	41	(8)	23	(9)
Mixed Non-Small Cell	11	(2)	2	(<1)
Other	46	(9)	21	(9)
Number of prior regimens				
1	243	(50)	121	(50)
2	238	(49)	119	(49)
3	7	(1)	3	(1)

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 compared with 4.7 months in the placebo group (see Figure 1). 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 HR for death in the Tarceva group relative to the placebo group was 0.73 (95% CI: 0.60 – 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.

Figure 1: **Kaplan-Meier Curve for Overall Survival of Patients by Treatment Group in Study BR.21**



The robustness of the overall survival result was examined in exploratory univariate analyses of a number of patient subsets formed according to stratification factors. The survival benefit with Tarceva treatment was seen across patient subsets including prior exposure to taxanes, smoking history, gender, age, histology, prior weight loss, time between initial diagnosis and randomisation and geographic location. The 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 0.82 among patients whose best response was stable disease or progressive disease.

Summarised in Table 5 are the results for study BR.21, including survival, time to deterioration of lung cancer-related symptoms and progression-free survival.

Table 5: Study BR.21- Efficacy Results

	Tarceva ***n*** **= 488**	**Placebo** ***n*** **= 243**	***p*-value**
Median survival	6.7 months	4.7 months	
Difference between survival curves			0.001
Hazard Ratio[a], mortality (erlotinib: placebo) **95% CI**	0.73 0.60 - 0.87		0.001
Median time to deterioration in cough[c]	6.4 months	3.6 months	0.041
Median time to deterioration in dyspnoea[c]	4.6 months	2.8 months	0.031[b]
Median time to deterioration in pain[c]	2.8 months	1.8 months	0.040[b]
Median progression-free survival	2.2 months	1.8 months	<0.001

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

[b] p-value adjusted for multiple testing

[c] from the EORTC QLQ-C30 and QLQ-LC13 quality of life questionnaires

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 medications in the Tarceva group.

The median PFS was 2.2 months in the Tarceva group compared with 1.8 months in the placebo group. The HR for progression, adjusted for stratification factors and HER1/EGFR status, was 0.61 (95% CI: 0.51 – 0.73; $p < 0.001$). The percent of PFS at 6 months was 24.5% and 9.3% respectively, for the Tarceva and placebo groups.

The objective response rate by RECIST in the Tarceva group was 8.9% (95% CI: 6.4 – 12.0). The median duration of response was 7.8 months, ranging from 2.2 months – 13.2+ months. Two responses (0.9%, 95% CI: 0.1 – 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 ($p = 0.004$).

In a double-blind, randomized phase III study (MO22162, CURRENTS) comparing two doses of Tarceva (300 mg vs 150 mg) in current smokers (mean of 38 pack years) with locally advanced or metastatic NSCLC in the second-line setting after failure on chemotherapy, the 300 mg dose of Tarceva demonstrated no PFS benefit over the recommended dose (7.00 vs 6.86 weeks, respectively). Patients in this study were not selected based on EGFR mutation status.

Pancreatic Cancer – Tarceva in Combination 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 (Study PA.3). Patients were randomised 1:1 to receive Tarceva (100 mg or 150 mg) or placebo once daily on a continuous schedule plus gemcitabine IV (1000 mg/m^2, Cycle 1 - days 1, 8, 15, 22, 29, 36 and 43 of an 8-week cycle; Cycle 2 and subsequent cycles - Days 1, 8 and 15 of a 4-week cycle (approved dose and schedule for pancreatic cancer according to gemcitabine product 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 except for a slightly larger proportion of females in the 100 mg Tarceva plus gemcitabine arm (51%) compared with the placebo plus gemcitabine 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) in Figure 2. The adjusted HR for death in the Tarceva group relative to the placebo group was 0.82 (95% CI: 0.69 – 0.98;p = 0.028). The percentage 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.

Figure 2: Kaplan-Meier curve for overall survival of patients in Tarceva 100mg dose cohort by treatment group in Study PA.3

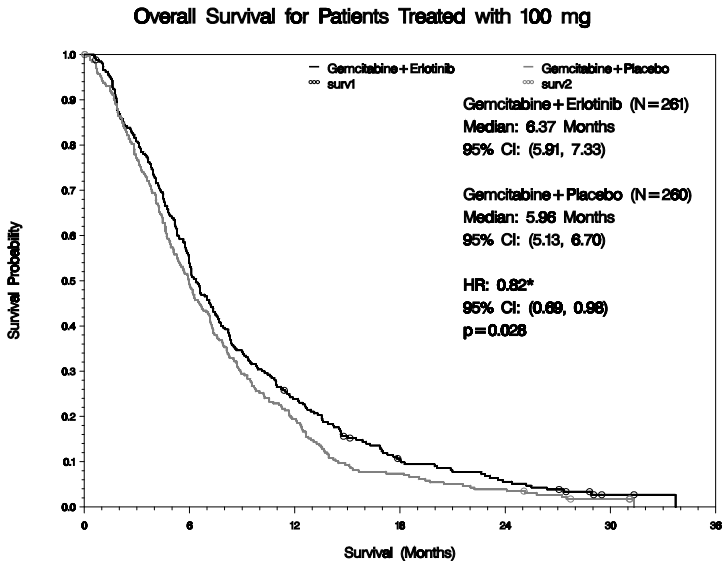


Table 6: Study PA.3 Efficacy Results

	Tarceva 100 mg plus gemcitabine (*n* = 261)	**Placebo plus gemcitabine (*n* = 260)**	***p*-value**
Median survival	6.4 months	6 months	
Hazard ratio, mortality (Tarceva:placebo) (95% CI)	0.82 (0.69 – 0.98)		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 – 4.93) compared with 3.55 months (15.2 weeks) in the placebo group (95% CI; 3.29 – 3.75; $p = 0.006$).

The median duration of response was 5.5 months, ranging from 0.85 months – 12.8+ months. 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 ($p = 0.036$).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Oral erlotinib is well absorbed 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 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]).

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% 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 of [^{14}C] labelled erlotinib in athymic nude mice with HN5 (head and neck carcinoma) tumour xenografts have shown rapid and extensive tissue distribution with maximum concentrations of radiolabeled drug in tumours (approximately 73% of that in plasma) and most other tissues observed to coincide with the peak plasma concentration.

Metabolism

Erlotinib is metabolised by the hepatic cytochromes in humans, primarily CYP3A4/ CYP3A5 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 3 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. They are present in plasma at levels that are < 10% of erlotinib and display similar pharmacokinetics to erlotinib. 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.

Excretion

A population pharmacokinetic analysis in 591 patients receiving single agent Tarceva (252 patients from Phase II studies A248-101, A248-1003, A248-1007 and OSI2288g; 339 patients from Phase III study BR.21) 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 and current smoking. Increased serum concentrations of total bilirubin and AAG 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 incorporating 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.

Following a 150 mg oral dose of Tarceva (591 patients – see above), at steady state, the median time to reach maximum plasma concentration is approximately 4 hours with median maximum plasma concentration achieved of 1 995 ng/mL. Prior to the next dose at 24 hours, the median minimum plasma concentration is 1 238 ng/mL. Median AUC achieved during the dosing interval at steady state is 41.3 μg.h/mL.

Pharmacokinetics in Special Populations

Hepatic impairment

Erlotinib is primarily 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.

The pharmacokinetics of erlotinib and its o-demethylated metabolites OSI-420 and OSI-413 were assessed in 36 patients with advanced solid tumours after a single 150 mg oral dose. Twenty-one patients had adequate hepatic function (total serum bilirubin ≤ upper limit of normal (ULN) and AST/AST ≤ 1.5 x ULN) and 15 had moderate hepatic impairment (Child-Pugh score 7 – 9).

Erlotinib and metabolite exposures were similar in the two groups, with geometric mean AUCs of 29 and 27 μg.h/mL for erlotinib in adequate and impaired hepatic function respectively and 2.0 and 2.4 μg.h/mL for metabolites respectively. However, the confidence intervals of the ratios of the AUCs were wide, so it could not be concluded that exposures were equivalent. The C_{max} of erlotinib was significantly lower in moderate hepatic impaired patients compared with those with adequate hepatic function consistent with delayed T_{max}. The differences in C_{max} and T_{max} are not clinically significant.

Renal impairment

Erlotinib and its metabolites are not significantly excreted by the kidneys (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 healthy non-smoking subjects and healthy subjects who currently smoke has shown that cigarette smoking leads to increased clearance of, and decreased exposure to, erlotinib. After a single 150 mg dose of erlotinib, the $AUC_{0\text{-infinity}}$ 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 (see section 5.1 Pharmacodynamic properties, Clinical trials), smokers achieved a median 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 smoked, 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. Median steady state trough plasma concentration at a 300 mg dose in smokers in this study was 1.22 μg/mL (*n* = 17) compared with 0.38 μg/mL (*n* = 15) at 150 mg**.** In a double-blind, randomized phase III study (MO22162, CURRENTS) comparing two doses of Tarceva (300 mg vs 150 mg) in

current smokers with locally advanced or metastatic NSCLC, a 300 mg dose did not show improved efficacy in second line treatment after failure of chemotherapy compared to the recommended 150 mg dose in patients who continue to smoke cigarettes (see section 5.1 Pharmacodynamic properties, Clinical trials).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Tarceva has been tested for genotoxicity in a series of *in vitro* assays (bacterial mutation, human lymphocyte chromosome aberration and mammalian cell mutation) and an *in vivo* mouse micronucleus test. Under the conditions of these assays, Tarceva did not cause genetic damage.

Carcinogenicity

In 2 year carcinogenicity studies, mice given daily oral doses of Tarceva at up to 60 mg/kg, female rats up to 5 mg/kg and male rats up to 10 mg/kg, did not show any evidence of tumourigenic potential. These doses were associated with Tarceva exposure levels approximately 10 and 1-2 times that anticipated clinically in mice and rats, respectively at the maximum recommended clinical dose.

Reproductive toxicity

When Tarceva was administered during organogenesis, reduced foetal/birth weight and increases in the incidence of small, incompletely inflated lung lobes and incomplete or absent ossification were observed in rats at doses that resulted in plasma concentrations comparable to those in humans. In rabbits, foetal weight was reduced at plasma concentrations 1.5 times those of humans and the incidence of absent ossification was increased at doses producing 4.5 times the clinical exposure. Embryo/foetal lethality and/or abortion was seen in rats and rabbits given doses that result in plasma drug concentrations 4.5 – 6.5 times those of humans. Embryo/foetal toxicity was associated with maternal toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose
Microcrystalline cellulose
Sodium starch glycollate
Sodium lauryl sulfate
Magnesium stearate

The tablets have a film-coating which contains:
Hypromellose
Hydroxypropylcellulose
Macrogol 400
Titanium dioxide

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Tarceva 25 mg, 100 mg and 150 mg film-coated tablets are available in PVC/Al blisters containing 30 tablets.

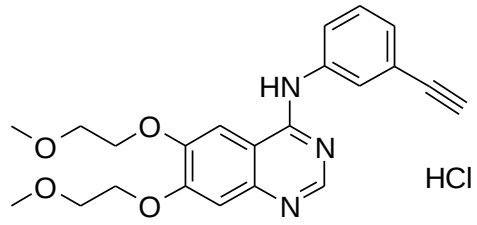
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure



Tarceva (erlotinib hydrochloride) is an epidermal growth factor receptor/human epidermal growth factor receptor type 1 (EGFR, also known as HER1) tyrosine kinase inhibitor. Erlotinib, the active ingredient of Tarceva, is a quinazolinamine with the chemical name N-(3- ethynylphenyl)- 6,7- bis(2- methoxyethoxy)- 4- quinazolinamine.

Erlotinib hydrochloride has the molecular formula $C_{22}H_{23}N_3O_4$. HCl and a molecular mass of 429.9. The molecule has a pK_a of 5.42 at 25ºC. Erlotinib hydrochloride is an off-white to pale yellow powder, it is sparingly soluble in water, slightly soluble in methanol and practically insoluble in acetonitrile, acetone, ethyl acetate and hexane.

Aqueous solubility of erlotinib hydrochloride is dependent on pH, with increased solubility at a pH < 5 due to protonation of the secondary amine. Over the pH range of 1.4 to 9.6, maximal solubility of approximately 0.4 mg/mL occurs at a pH of approximately 2.

CAS Number: 183319-69-9

7. POISONS STANDARD

Schedule 4 – Prescription only medicine.

8. SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30 – 34 Hickson Road

Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

30 January 2006

10. DATE OF REVISION OF THE TEXT

31 August 2022

Summary of Changes Table

Section Changed	Summary of new information
4.5	Typographical correction
5.1	Change to ATC Code