Tarceva®

Erlotinib

COMPOSITION

Active substance: erlotinib as erlotinib hydrochloride

Excipients: Cellulose microcrystalline, Lactose monohydrate, Sodium starch glycolate, Magnesium stearate, Sodium laurilsulfate, Hypromellose, Hydroxypropyl cellulose, Titanium dioxide, Macrogol 400, Printing ink (shellac, iron oxide red, propylene glycol) for 100 mg or Printing ink (shellac, iron oxide black, Iron oxide yellow, propylene glycol) for 150 mg

GALENICAL FORM AND AMOUNT OF ACTIVE INGREDIENT PER UNIT

25 mg, 100 mg and 150 mg film-coated tablets.

INDICATIONS AND POTENTIAL USES

Tarceva is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen.

For maintenance treatment in patients with locally advanced or metastatic NSCLC after 4 cycles of standard platinum-based first-line chemotherapy where the disease is not progressing and has failed to respond adequately to chemotherapy.

Tarceva is indicated for the first-line treatment of patients with locally advanced or metastatic NSCLC with EGFR-activating mutations.

DOSAGE AND ADMINISTRATION

General

It is mandatory for Tarceva treatment to be initiated under the supervision of a physician with experience in treating cancer patients.

Patients with locally advanced or metastatic NSCLC should be tested for EGFR mutation status prior to first-line or maintenance therapy with Tarceva. EGFR mutations must be demonstrated using a validated test.

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

If dose reduction is necessary, reduce in 50 mg steps (see "Warnings and precautions").

Dose reduction is necessary when Tarceva is used concomitantly with CYP3A4 inhibitors (see "Interactions").

See "Interactions" regarding concomitant use with proton pump inhibitors, H_2 antagonists or antacids.

Special dosage instructions

Hepatic impairment

Erlotinib is principally metabolised in the liver and eliminated in the bile (see "Pharmacokinetics"). Erlotinib exposure in patients with moderately impaired hepatic function (Child-Pugh score 7–9) was similar to that in patients with normal hepatic function. Tarceva should nevertheless be administered with caution to patients with elevated transaminases. In the event of severe undesirable effects, the dose should be reduced or Tarceva therapy interrupted (see "Warnings and precautions"). The safety and efficacy of Tarceva have not been studied in patients with cirrhosis or extensive liver metastases (see "Warnings and precautions").

Renal impairment

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

Pediatric use

The safety and efficacy of Tarceva in the approved indications have not been studied in patients under the age of 18 years.

CONTRAINDICATIONS

Hypersensitivity to the active substance or any of the excipients.

WARNINGS AND PRECAUTIONS

Interstitial lung disease

Rare cases of interstitial lung disease (ILD), including fatalities, have been reported in patients receiving Tarceva for treatment of non-small cell lung cancer (NSCLC) or other advanced solid tumours. In a meta-analysis of randomized controlled clinical trials of EGFR-TKIs in NSCLC, the incidence of ILD-like events was 0.9% on treatment with Tarceva and 0.4% in the control arms. The overall incidence of ILD events in the patients treated with the EGFR-TKIs used in this meta-analysis was 1.2% and the relative risk of death in this group compared to controls was 1.96. The overall incidence in Tarceva-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) was approximately 0.6%. Reported diagnoses in patients suspected of having ILD included for example pneumonitis and alveolitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome (ARDS) and lung infiltration. Most of the cases were associated with additional factors such as concomitant or prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, lung metastases or pulmonary

infections. In patients with acute onset of new and/or unexplained progressive pulmonary symptoms such as dyspnea, 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.

Diarrhea, dehydration, electrolyte imbalance and renal failure

Diarrhea has occurred in patients on Tarceva and, if moderate or severe, should be treated with loperamide. In some cases dose reduction may be necessary. In the event of severe or persistent diarrhea, nausea, anorexia or vomiting associated with dehydration, Tarceva therapy should be interrupted and appropriate measures taken to treat the dehydration. This is especially true in the presence of aggravating risk factors (medications, symptoms or diseases or other predisposing factors such as advanced age). After careful preliminary assessment, intravenous rehydration should be considered. There have been rare reports of hypokalemia and renal failure (including fatalities). Some reports of renal failure were associated with severe dehydration, chiefly in patients treated with loperamide for diarrhea or secondary to vomiting and/or anorexia, while in other cases, concomitant chemotherapy played a role. Patients at risk of dehydration should additionally be monitored for renal function and serum electrolytes, including potassium.

Data on the effect of Tarceva therapy on QT prolongation are limited. An electrocardiogram should be recorded before starting treatment. Treatment should be undertaken only with caution in patients with pre-existing QT prolongation or treated concomitantly with QT-prolonging medications.

Tarceva should be used with caution in patients with elevated transaminases. The safety and efficacy of Tarceva have not been studied in patients with cirrhosis or extensive liver metastases.

Hepatitis, hepatic failure

Rare cases of hepatic failure (including fatalities) have been reported during use of Tarceva. Confounding risk factors were pre-existing liver disease or concomitant hepatotoxic medications. Regular liver function testing should therefore be considered in such patients. Treatment with Tarceva should be interrupted if changes in liver function are severe.

Gastrointestinal perforation: Patients receiving Tarceva are at increased risk of developing gastrointestinal perforation. This risk is increased in patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs and/or taxane-based chemotherapy, or who have prior history of peptic ulceration or diverticular disease. Tarceva should be permanently discontinued in patients who develop gastrointestinal perforation.

Bullous and exfoliative skin disorders: Bullous and exfoliative skin changes have been reported, including very rare cases of suspected Stevens-Johnson syndrome/toxic epidermal necrolysis, which were sometimes fatal. Tarceva treatment should be interrupted or discontinued if the patient develops severe bullous or exfoliative skin changes.

Ocular disorders: Very rare cases of corneal perforation or ulceration have been reported during use of Tarceva. Other ocular disorders that are also risk factors for corneal perforation/ulceration, including abnormal eyelash growth, keratoconjunctivitis sicca and keratitis, have been observed with Tarceva treatment. Tarceva treatment should be interrupted or discontinued in patients with acute or progressive ocular disorders such as eye pain.

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

Erlotinib is a weak inhibitor of glucuronidation. Patients with glucuronidation disorders (e.g. Gilbert's disease) must therefore be treated with caution.

INTERACTIONS

CYP3A4/CYP1A2 inhibitors: The CYP3A4 inhibitor ketoconazole (200 mg orally twice daily for 5 days) increased the AUC of erlotinib by 86% and C_{max} by 69%. When Tarceva was coadministered with ciprofloxacin, an inhibitor of CYP3A4 and CYP1A2, erlotinib exposure (AUC) and maximum serum level (C_{max}) increased by 39% and 17%, respectively. Caution should therefore be exercised and the dose reduced when administering Tarceva with CYP3A4 inhibitors or combined CYP3A4/CYP1A2 inhibitors (see "Dosage and administration").

CYP3A4 inducers: Potent inducers of CYP3A4 activity increase erlotinib metabolism and significantly decrease erlotinib plasma concentrations. Thus induction of CYP3A4 metabolism by rifampicin (600 mg orally once daily for 7 days) resulted in a 69% decrease in the median erlotinib AUC following a 150 mg dose of Tarceva as compared to Tarceva alone. Coadministration with potent CYP3A4 inducers should be avoided wherever possible.

Tarceva is not a CYP3A4 inhibitor. In patient studies no change was observed in the metabolism of erythromycin (breath test) or midazolam during comedication with erlotinib. The oral bioavailability of midazolam decreased by 24% over 14 days on comedication with erlotinib. The mechanism has not been elucidated.

The solubility of erlotinib is pH-dependent, decreasing with increasing pH. Medicines that alter the pH of the upper gastrointestinal tract may alter the solubility of erlotinib and hence its bioavailability.

Proton pump inhibitors: Coadministration of Tarceva with omeprazole, a proton pump inhibitor, halved Tarceva bioavailability (AUC ratio 0.54; 90% CI, 0.49 – 0.59; C_{max} ratio 0.39; 90% CI, 0.32 – 0.48). There were relatively large variations in t_{max}. Coadministration of Tarceva with proton pump inhibitors should be avoided.

H_2 antagonists: 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. Coadministration of Tarceva with medicines that reduce gastric acid production should therefore be avoided where possible. Increasing the dose of Tarceva when coadministered 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 twice daily, erlotinib exposure [AUC] and C_{max} decreased by only 15% and 17%, respectively. If patients need to be treated with such medicines, then an H_2 antagonist such as ranitidine should be considered and administered in a staggered manner. Tarceva must be taken at least 2 hours before or 10 hours after the H_2 antagonist.

Antacids: The effects of coadministration of erlotinib and antacids are unknown. Concomitant use of these combinations should therefore be avoided. If use of antacids is considered necessary during treatment with Tarceva, they should be taken at least 4 hours before or 2 hours after the daily dose of Tarceva.

Anticoagulants: International Normalised Ratio (INR) elevations and bleeding events, in some cases fatal, have been observed during concomitant administration of Tarceva and coumarin-derivative anticoagulants. Patients taking warfarin or other coumarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR.

Combination of Tarceva with statins increases the risk of myopathy, including rhabdomyolysis, which was observed rarely.

Smoking induces CYP1A1 and CYP1A2, leading in smokers to a 50–60% reduction in erlotinib exposure. Smokers should therefore be advised to stop smoking (see "Dosage and administration, Special dosage instructions".

PREGNANCY AND LACTATION

Females and males of reproductive potential

Contraception: Effective contraception should be practiced during therapy and for at least 2 weeks after completing therapy.

Pregnancy

There are no adequate or well-controlled studies in pregnant women using Tarceva. Studies in animals have shown some reproductive toxicity (see "Preclinical data"). The potential risk for humans is unknown. Women of childbearing potential must be advised to avoid pregnancy while taking Tarceva.

Lactation

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Based on its pharmacological properties, erlotinib is likely to have no or negligible influence on the ability to drive and use machines. No relevant studies have been

performed. Because of side effects such as nausea, vomiting, and fatigue however, caution is required when driving vehicles and operating machinery.

UNDESIRABLE EFFECTS

The commonest adverse events are rash (75%) and diarrhea (54%). These are mostly grade 1 or 2 in severity and do not require treatment. Grade 3 and 4 rash and diarrhea occur in 9% and 6% of patients, respectively. Each led to study discontinuation in 1% of patients. Dose reduction for rash and diarrhea was needed in 6% and 1% of patients, respectively. Rash and diarrhea generally occur, respectively, 8 and 12 days after the start of treatment.

Adverse drug reactions are listed according to MedDRA system organ class. The frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000).

Infections and infestations

Very common: infection (24%, grade 3: 4%, grade 4: 0%). Severe infections, with or without neutropenia, have included pneumonia, sepsis and cellulitis.

Metabolism and nutrition disorders

Very common: anorexia (52%, grade 3: 8%, grade 4: 1%).

Eye disorders

Very common: conjunctivitis (12%, grade 3: <1%, grade 4: 0%), keratoconjunctivitis sicca (12%, grade 3: 0%, grade 4: 0%).

Common: keratitis.

Very rare: corneal ulceration and perforation (see "Warnings and precautions"). Abnormal eyelash growth, including ingrowing eyelashes, excessive growth and thickening of the eyelashes, has been reported in isolated cases. Cases of uveitis have been reported in post-marketing surveillance.

Respiratory, thoracic and mediastinal disorders

Very common: dyspnea (41%, grade 3: 17%, grade 4: 11%), cough (33%, grade 3: 4%, grade 4: 0%).

Rare: interstitial lung disease, in some cases fatal.

Gastrointestinal disorders

Very common: diarrhea (54%, grade 3: 6%, grade 4: <1%), nausea (33%, grade 3: 3%, grade 4: 0%), vomiting (23%, grade 3: 2%, grade 4: <1%), stomatitis (17%, grade 3: <1%, grade 4: 0%), abdominal pain (11%, grade 3: 2%, grade 4: <1%).

Common: gastrointestinal bleeding.

Uncommon: gastrointestinal perforation, in some cases with fatal outcome (see "Warnings and precautions").

Hepatobiliary disorders*Common:* elevated ALT and AST levels, elevated bilirubin.

Rare: cases of hepatic failure (including fatalities).

Skin and subcutaneous tissue disorders*Very common:* rash, generally erythematous and papulopustular, mild to moderate, particularly on exposure to sunlight (75%, grade 3: 8%, grade 4: <1%), pruritus (13%, grade 3: <1%, grade 4: 0%), dry skin (12%, grade 3: 0%, grade 4: 0%). Patients heavily exposed to sunlight should protect themselves accordingly (e.g. clothing, sunscreen).

Common: paronychia; skin fissures, mostly non-serious; acne; dermatitis acneiform; folliculitis, mostly mild and non-serious.

Uncommon: hirsutism, hyperpigmentation, eyelash/eyebrow changes and brittle and loose nails.

Very rare: bullous and exfoliative skin changes, including cases of suspected Stevens-Johnson syndrome/toxic epidermal necrolysis, which were sometimes fatal (see "Warnings and precautions").

Renal and urinary disorders

Rare: renal failure (related and unrelated to dehydration).

General disorders and administration site conditions

Very common: fatigue (52%, grade 3: 14%, grade 4: 4%).

OVERDOSAGE

Single oral doses of Tarceva up to 1000 mg in healthy subjects and up to 1600 mg in cancer patients have been tolerated. Repeated administration of 200 mg Tarceva twice daily to healthy subjects was poorly tolerated after only a few days of treatment. Based on the data from these studies, severe undesirable effects such as diarrhea, rash and possibly liver transaminase elevation may occur above the recommended dose of 150 mg daily. In case of suspected overdose, Tarceva should be withheld and symptomatic treatment initiated.

PROPERTIES/EFFECTS

ATC code: L01XE03

Mechanism of action and pharmacodynamics

Erlotinib is an epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor. HER1/EGFR is expressed on the surface of normal cells and cancer cells. In non-clinical

models, inhibition of HER1/EGFR tyrosine kinase results in cell stasis and/or death. No studies are yet available on the effect in tumour tissue.

Clinical efficacy

First-line therapy for patients with EGFR-activating mutations

The efficacy of Tarceva in first-line treatment of patients with EGFR-activating mutations in NSCLC was demonstrated in a phase III, randomised, open-label trial (ML20650, EURTAC). This study was conducted in Caucasian patients with metastatic or locally advanced NSCLC (stage IIIB and IV) who had not received previous chemotherapy or any systemic antitumour therapy for their advanced disease and who presented 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 daily or platinum-based doublet chemotherapy.

The primary endpoint was investigator-assessed progression-free survival (PFS). The efficacy results are summarised in Table 1.

Table 1 Efficacy results of Tarceva versus chemotherapy in trial ML20650 (EURTAC)

		Tarceva	Chemo-therapy	Hazard ratio (95% CI)	p-value
Pre-planned interim analysis (35% OS maturity) (n=153) Cut-off date: 2 August 2010		n=77	n=76		
	Primary endpoint: progression-free survival (PFS, median in months)*				
	Investigator-assessed**	9.4	5.2	0.42 [0.27-0.64]	p<0.0001
	Independent review**	10.4	5.4	0.47 [0.27-0.78]	p=0.003
	Best overall response rate (CR/PR)	54.5%	10.5%		p<0.0001
	Overall survival (OS) (months)	22.9 [0.1-36.4]	18.8 [0-35.3]	0.80 [0.47-1.37]	p=0.4170
Final analysis of PFS (62% OS maturity) (n=173) Cut-off date: 11 April 2012		n=86	n=87		
	PFS (median in months)	10.4	5.1	0.34 [0.23-0.49]	p<0.0001
	OS*** (months)	22.9 [0.1-58.2]	20.8 [0-44.0]	0.93 [0.64-1.36]	p=0.7149

CR=complete response; PR=partial response

* A 58% reduction in the risk of disease progression or death was observed.

** Overall concordance rate between investigator and IRC assessment was 70%.

*** High crossover was observed, with 82% of the patients in the chemotherapy arm receiving subsequent therapy with an EGFR tyrosine kinase inhibitor (all but 2 of these patients were subsequently treated with Tarceva).

There were few smokers/ex-smokers in the EURTAC study. No significant benefit was shown in the smoker subgroup (n=13; HR=0.92; 95% CI, 0.23 to 3.74) or ex-smoker subgroup (n=30; HR=0.90; 95% CI, 0.32 to 2.57).

Median PFS in the exon 19 deletion subgroup was 5.1 months in the chemotherapy arm (n=48) versus 10.4 months in the Tarceva arm (n=49) (HR=0.31; 95% CI, 0.18 to 0.55). Median PFS in the exon 21 mutation subgroup was 5.5 months in the chemotherapy arm (n=28) versus 8.3 months in the Tarceva arm (n=28) (HR=0.65; 95% CI, 0.33 to 1.27).

Additional published data

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

An analysis of pooled published data in NSCLC patients showed a longer mean PFS in patients with tumours with EGFR-activating mutations receiving Tarceva as primary first-line therapy (n=70; 12.5 months; 95% CI, 10.6 to 16.0) than in patients treated with chemotherapy (n=359; 6.0 months; 95% CI, 5.4 to 6.7).

Maintenance therapy after platinum-based first-line chemotherapy

The efficacy and safety of Tarceva as maintenance therapy after first-line chemotherapy for NSCLC were investigated in a randomised, placebo-controlled, double-blind trial (BO18192, SATURN). This study was conducted in 889 patients with locally advanced or metastatic NSCLC whose disease activity did not progress after 4 cycles of platinum-based doublet chemotherapy. Patients were randomised 1:1 to receive Tarceva 150 mg or placebo orally once daily until disease progression. The primary endpoint of the study was PFS in all patients and in patients with an EGFR IHC-positive tumour. Baseline demographic and disease characteristics were well balanced between the two treatment arms. Patients with ECOG performance status >1 or significant hepatic or renal comorbidity were not included in the clinical study.

Overall study

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

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

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

Patients with EGFR-activating mutations had the largest treatment benefit (n=49; PFS HR=0.10; 95% CI, 0.04 to 0.25; p<0.0001). In patients with EGFR wild-type tumours (n=388), the PFS HR was 0.78 (95% CI, 0.63 to 0.96; p=0.0185) and the OS HR was 0.77 (95% CI, 0.61 to 0.97; p=0.0243).

Patients with stable disease after platinum-based chemotherapy

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

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

Second- and third-line therapy

In a double-blind controlled study, 731 patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) were treated with Tarceva 150 mg or placebo once daily after failure of at least one previous chemotherapy. Half the patients had one, and the other half two prior chemotherapies; 92% had previously been exposed to a platinum-based regimen; 36% had previously received taxanes. The primary endpoint, overall survival, showed a significant advantage for erlotinib: median survival was 6.7 months (95% CI, 5.5 to 7.8) with erlotinib *vs* 4.7 months (95% CI, 4.1 to 6.3) with placebo, p=0.002. There were likewise significant differences in progression-free survival and objective response rate (8.9% in the erlotinib group *vs* 1% in the placebo group). Significant differences were also seen in the course of the quality parameters cough, pain and dyspnea (EORTC QLQ-LC13). In a Cox regression analysis of the relevant independent variables, a more favourable disease course was associated with smoker status, in the case of survival, and with rash in an exploratory analysis of response.

In a small uncontrolled study in 55 patients the response rate was 12.3% and overall survival 8.4 months (95% CI, 4.8 to13.9). Survival was again correlated with rash.

Two studies of first-line treatment in metastatic NSCLC in combination, respectively, with paclitaxel plus carboplatin and gemcitabine plus cisplatin showed no significant effect, but increased undesirable effects, with erlotinib. Combination of erlotinib with cytostatics has thus not been adequately studied.

PHARMACOKINETICS

Absorption

After oral administration of erlotinib, t_{max} is approximately 4 hours. Absolute bioavailability could not be exactly determined; it is between 60% and 106%. Taking erlotinib together with food increases its AUC by 34–109%.

Distribution

Erlotinib is 95% bound to plasma protein (albumin and α-1-glycoprotein) and has a mean volume of distribution of 232 l.

Metabolism

Erlotinib is metabolised in the liver by CYP3A4 and CYP1A2 and in the lungs possibly by CYP1A1. *In vitro* studies indicate that approximately 70% of erlotinib metabolism is by CYP3A4. Three main metabolic pathways have been 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; 3) aromatic hydroxylation of the phenyl-acetylene moiety. The main metabolites of erlotinib produced by O-demethylation of either side chain showed similar efficacy to erlotinib in non-clinical *in vitro* studies and *in vivo* tumour models. They are present in plasma at levels that are <10% of erlotinib and display similar pharmacokinetics to erlotinib.

Elimination

Over 90% of an erlotinib dose is excreted in the feces, mainly in the form of metabolites. Clearance is 4.47 l/h and half-life 36.2 hours.

Pharmacokinetics in special patient populations

No significant relationships were observed between predicted apparent clearance and patient age, body weight, gender and ethnicity.

Pediatric and geriatric use

There have been no specific studies in pediatric or geriatric patients.

Hepatic impairment

Erlotinib exposure in patients with moderately impaired hepatic function (Child-Pugh score 7–9) was similar to that in patients with normal hepatic function, including patients with primary liver cancer or hepatic metastases.

Renal impairment

No clinical studies have been conducted in patients with compromised renal function.

Smokers

In a pharmacokinetic study in healthy subjects, $AUC_{0-\infty}$ was half to a third of the value found in non-smokers/ex-smokers owing to induction of CYP1A1 in the lungs and CYP1A2 in the liver.

Erlotinib clearance is increased 2.8-fold in smokers.

PRECLINICAL DATA

Carcinogenicity

Preclinical studies showed no evidence of carcinogenic potential. Erlotinib was neither genotoxic nor clastogenic in genotoxicity studies. Two-year carcinogenicity studies with erlotinib conducted in rats and mice were negative at exposures exceeding therapeutic use in humans.

Mutagenicity

Erlotinib was negative in the standard battery of genotoxicity assays.

Impairment of fertility

Impairment of fertility was not observed in male and female rats at doses near the maximum tolerated dose (MTD).

Teratogenicity

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

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.

Other

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

An *in vivo* phototoxicity study with erlotinib in rats showed phototoxic potential in the form of mild erythema.

Photosensitisation was performed in guinea pigs and produced no evidence of photoallergenicity.

SPECIAL REMARKS

Stability

Tarceva should not be used after the expiry date (EXP) shown on the pack.

Disposal

Any medicinal products unused after the end of treatment or by the expiry date should be returned in their original packaging to the place of supply (physician or pharmacist) for proper disposal.

Storage

Do not store above 30°C.

Packs

25 mg film-coated tablets	30
100 mg film-coated tablets	30
150 mg film-coated tablets	30

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

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