

PRODUCT MONOGRAPH

Pr **TARCEVA**[®]

erlotinib hydrochloride tablets

erlotinib 25, 100, 150 mg

Pharmaceutical standard: Professed

Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor

Hoffmann-La Roche Limited
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TARCEVA[®]
(erlotinib hydrochloride)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients*
Oral	Tablet/25 mg, 100 mg, 150 mg	Lactose monohydrate

**For a complete list of ingredients see Dosage Forms, Composition and Packaging section*

INDICATIONS AND CLINICAL USE

TARCEVA[®] (erlotinib) is indicated as monotherapy 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, and whose EGFR expression status is positive or unknown. [see *Clinical Trials* section - *Relation of Results to EGFR Protein Expression Status (as Determined by Immunohistochemistry)*]

TARCEVA should be administered under the supervision of a qualified health professional who is experienced in the treatment and management of patients with cancer.

Geriatrics (> 65 years of age):

There have been no specific studies in elderly patients. Of the total number of patients participating in the phase III study, BR.21 (n=731), 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. No meaningful differences in safety or pharmacokinetics were observed between younger and older patients. Therefore, no dosage adjustments are recommended in elderly patients.

Paediatrics:

The safety and efficacy of TARCEVA in the pediatric population has not been established.

CONTRAINDICATIONS

TARCEVA (erlotinib) is contraindicated in patients with severe hypersensitivity to erlotinib or to any component of TARCEVA. For a complete listing, see the *Dosage Forms, Composition and Packaging* section.

WARNINGS AND PRECAUTIONS

Drug Interactions

Erlotinib is metabolized 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 drugs which are metabolized by, or are inhibitors or inducers of, these enzymes (see *Drug Interactions* section).

Gastrointestinal

Diarrhea, Dehydration, Electrolyte Imbalance and Renal Failure:

Diarrhea has occurred in patients on TARCEVA (erlotinib) and moderate or severe diarrhea 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 should be taken to treat the dehydration (see *Dosage and Administration* section).

There have been rare reports of hypokalaemia and renal failure (including fatalities) mainly in patients receiving concomitant chemotherapy but also in a few patients receiving TARCEVA as monotherapy. Some reports of renal failure were secondary to severe dehydration due to diarrhea, vomiting and/or anorexia while others were confounded by concomitant use of chemotherapy. In more severe or persistent cases of diarrhea, or cases leading to dehydration, particularly in groups of patients with aggravating risk factors (known renal disease, concurrent vomiting, 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 high risk of dehydration.

Gastrointestinal bleeding was seen in 2% of patients receiving TARCEVA therapy on study BR.21 in NSCLC. No cases were reported on the placebo arm. Confounding factors include concomitant NSAID use and history of ulcer disease. In patients who develop gastrointestinal bleeding while receiving TARCEVA, the drug should be discontinued (see *Adverse Reactions–Clinical Trial Adverse Drug Reactions - Gastrointestinal disorders*

Hepatotoxicity

Asymptomatic increases in liver transaminases have been observed in patients receiving TARCEVA. Therefore, periodic liver function testing (transaminases, bilirubin, and alkaline phosphatase) should be considered. Dose reduction or interruption of TARCEVA therapy should be considered if liver function changes are severe (see *Adverse Reactions* section).

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

Rash

In pivotal trial BR.21, over three quarters of patients developed a rash. Nine percent (9%) of patients had severe rash, and 6% required dose reduction. Median time to onset of rash was 8 days.

Respiratory

Interstitial Lung Disease (ILD): Cases of ILD-like events, including fatalities, have been reported uncommonly in patients receiving TARCEVA for treatment of NSCLC or other advanced solid tumours. In the pivotal study BR.21 in NSCLC, the incidence of serious ILD-like events was 0.8% in both the TARCEVA and placebo arms. The overall incidence in TARCEVA treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) is approximately 0.6%. Some examples of reported diagnoses in patients suspected of having ILD-like events include pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome, lung infiltration and alveolitis. Symptoms started from 5 days to more than 9 months (median 47 days) after initiating TARCEVA. 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 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 (see *Adverse Reactions/Dosage and Administration* sections).

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.

Special Populations

Patients with Brain Metastases: Pivotal trial BR.21 excluded patients with CNS metastases that were symptomatic, and those with asymptomatic metastases but not on a stable dose of corticosteroids for at least 4 weeks prior to randomization. Therefore, the safety of TARCEVA in this patient population is unknown.

Pregnant Women: There are no adequate or well-controlled studies in pregnant women using TARCEVA. Studies in animals have shown reproductive toxicity (see *Toxicology* section). 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 fetus. If TARCEVA is used during pregnancy, the patient must be informed of the potential hazard to the fetus or potential risk for loss of the pregnancy.

Nursing Women: 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.

Patients with Hepatic Impairment: TARCEVA is eliminated by hepatic metabolism and biliary excretion. The safety and efficacy of TARCEVA has not been studied in patients with hepatic impairment. In pivotal trial BR.21, adequate hepatic function was defined as total bilirubin < 1.5 x ULN and ALT/SGPT < 2x ULN, unless clearly attributable to liver metastases, in which cases < 5 x ULN was allowed. Approximately 20% of patients on BR.21 had liver metastases. Asymptomatic increases in liver transaminases have been observed in TARCEVA treated patients; therefore, periodic liver function testing (transaminases, bilirubin, and alkaline phosphatase) should be considered. Dose reduction or interruption of TARCEVA should be considered if changes in liver function are severe (see *Adverse Reactions* section – *Abnormal Hematologic and Clinical Chemistry Findings*).

Monitoring and Laboratory Tests

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

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

In one randomized double-blind study (BR.21) conducted in 17 countries, 731 patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen were randomized 2:1 to receive TARCEVA (erlotinib) 150 mg or placebo. Study drug was taken orally once daily until disease progression or unacceptable toxicity.

Rash (75%) and diarrhea (54%) were the most common adverse events regardless of causality. Most were Grade 1 or Grade 2 in severity and manageable without intervention. Grade 3/4 rash and diarrhea occurred in 9% and 6%, respectively in TARCEVA-treated patients and each resulted in study discontinuation in 1% of patients. Dose reduction for rash and diarrhea 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 diarrhea was 12 days.

In pivotal trial BR.21, serious gastrointestinal hemorrhage was seen in 8 TARCEVA treated patients (2%) and there were no cases in placebo treated patients. The gastrointestinal hemorrhage was fatal in 2 patients treated with TARCEVA. Confounding factors include concomitant NSAID use and history of peptic ulcer disease. The incidence of serious interstitial

lung disease in BR.21 was 0.8% in each treatment arm. There was 1 case of fatal pneumonitis (fatal outcome of ILD) in each treatment arm.

Adverse events occurring more frequently ($\geq 3\%$) in TARCEVA-treated patients than in the placebo arm in the pivotal study BR.21, and in at least 10% of patients in the TARCEVA arm, are summarized by NCI-CTC Grade in **Table 1**. Listed events are adverse reactions attributed to TARCEVA therapy.

Table 1: Adverse events 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 N=485			Placebo N=242		
	Any Grade	3	4	Any Grade	3	4
MedDRA Preferred Term	%	%	%	%	%	%
Total patients with any AE	99	40	22	96	36	22
<i>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>Gastrointestinal disorders</i>						
Diarrhea	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>General disorders and administration site conditions</i>						
Fatigue	52	14	4	45	16	4
<i>Metabolism and nutrition disorders</i>						
Anorexia	52	8	1	38	5	<1
<i>Respiratory, thoracic and mediastinal disorders</i>						
Dyspnea	41	17	11	35	15	11
Cough	33	4	0	29	2	0
<i>Infections and infestations</i>						
Infection	24	4	0	15	2	0
<i>Eye disorders</i>						
Conjunctivitis	12	<1	0	2	<1	0
Keratoconjunctivitis sicca	12	0	0	3	0	0

Other Observations:

The primary safety population was defined as the 856 patients treated with at least one 150 mg dose of TARCEVA monotherapy during Phase II and Phase III studies in NSCLC (A248-1007, BR.21) and other Phase I through II studies in populations other than NSCLC. This population also takes into consideration the 242 patients who received placebo in study BR.21. The following common and uncommon adverse reactions have been observed in patients who received TARCEVA monotherapy in the primary safety population.

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

Gastrointestinal disorders: Cases of gastrointestinal bleeding have been commonly reported in clinical studies, some associated with concomitant warfarin administration (see also *Drug Interactions* section) and some with concomitant NSAID administration.

Eye disorders: Keratitis has been reported commonly in clinical trials of TARCEVA. Corneal ulcerations may occur. Corneal ulcerations have been reported very rarely in patients receiving TARCEVA as a complication of mucocutaneous inflammation.

Skin and subcutaneous tissue disorders: 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.

Abnormal Hematologic and Clinical Chemistry Findings

Hepato-biliary disorders: Liver function test abnormalities (including elevated alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin) have been observed commonly. These were mainly mild or moderate in severity, transient in nature or associated with liver metastases]. Rare cases of hepatic failure (including fatalities) have been reported during use of TARCEVA. Confounding factors in some cases have included pre-existing liver disease or concomitant hepatotoxic medications (see *Warnings and Precautions* section). Grade 2 (> 2.5 -5.0 x ULN) ALT elevations occurred in 4% and < 1% of TARCEVA and placebo treated patients, respectively. Grade 3 (< 5.0- 20.0 x ULN) elevations were not observed in TARCEVA treated patients. Dose reduction or interruption of TARCEVA should be considered if changes in liver function are severe (see *Dosage and Administration* section).

Less Common Clinical Trial Adverse Drug Reactions (<1%)

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* section).

Post-Market Adverse Drug Reactions

Skin and subcutaneous tissue disorders: Hair and nail changes, mostly non-serious, were reported uncommonly from post-marketing surveillance, e.g. hirsutism, eyelash/eyebrow changes, paronychia and brittle and loose nails.

DRUG INTERACTIONS

Overview

Erlotinib is metabolized 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 drugs which are metabolized by, or are inhibitors or inducers of, these enzymes.

Drug-Drug Interactions

Comprehensive testing of drug-drug interactions with TARCEVA (erlotinib) has not been done.

Potent inhibitors of CYP3A4 activity decrease erlotinib metabolism and increase erlotinib plasma concentrations. Inhibition of CYP3A4 metabolism by ketoconazole (200 mg po BID for 5 days) resulted in increased exposure to erlotinib (86% in median erlotinib exposure [AUC]) and a 69% increase in 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 maximum concentration (C_{max}) increased by 39% and 17%, respectively. Therefore caution should be used when administering TARCEVA with potent CYP3A4 or combined CYP3A4/CYP1A2 inhibitors. These include, but are not limited to, calcium channel blockers (eg. diltiazem, verapamil); antifungals (eg. ketoconazole, fluconazole, itraconazole, voriconazole); macrolide antibiotics (eg. erythromycin, clarithromycin); fluoroquinolone antibiotics (eg. ciprofloxacin, norfloxacin); some HIV antivirals (eg. ritonavir, indinavir); and grapefruit juice. In these situations, the dose of TARCEVA should be reduced if toxicity is observed (see *Dosage and Administration* section).

Potent inducers of CYP3A4 activity increase erlotinib metabolism and significantly decrease erlotinib plasma concentrations. Induction of CYP3A4 metabolism by rifampicin (600 mg po QD 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. Other CYP3A4 inducers include, but are not limited to, barbiturates (eg. phenobarbital); anticonvulsants (eg. carbamazepine, phenytoin); glucocorticoids; pioglitazone; St. John's Wort, and some HIV antivirals (eg. efavirenz, nevirapine). Alternate treatments lacking potent CYP3A4 inducing activity should be considered when possible.

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 erlotinib is pH dependent. Erlotinib solubility decreases as pH increases. 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. Therefore, drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and hence its bioavailability. Increasing the dose of TARCEVA when co-administered with such agents is not likely to compensate for this loss of exposure.

International Normalized Ratio (INR) elevations and bleeding events including gastrointestinal bleeding (see *Warnings and Precautions/Adverse Reactions* sections) 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 any changes in prothrombin time or INR.

Drug-Food Interactions

Grapefruit juice has CYP3A4 inhibitory activity, therefore ingestion of grapefruit juice while on TARCEVA therapy may lead to decreased erlotinib metabolism and increased erlotinib plasma concentrations (see *Drug - Drug Interactions*).

Drug-Herb Interactions

St. John's Wort is a potent CYP3A4 inducer. Co-administration with erlotinib can lead to increased erlotinib metabolism and decreased erlotinib plasma concentrations (see *Drug - Drug Interactions*).

Drug-Lifestyle Interactions

Based on population pharmacokinetic data, smokers had a 24% higher rate of erlotinib clearance.

DOSAGE AND ADMINISTRATION

The recommended daily dose of TARCEVA (erlotinib) is 150 mg taken orally with a glass of plain water, at least one hour before or two hours after the ingestion of food.

Dosage Adjustment

When dose reduction is necessary, it is recommended to reduce in 50 mg steps.

Diarrhea can mostly be managed by loperamide. Patients with severe diarrhea that are unresponsive to loperamide or associated with dehydration may require a dose reduction or temporary interruption of therapy. Patients with severe skin reactions may also require a dose reduction or temporary interruption of therapy (see *Warnings and Precautions* section).

In patients who develop acute onset of new and/or progressive unexplained 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 (see *Warnings and Precautions* section).

In patients being concomitantly treated with a potent CYP3A4 inhibitor such as, but not limited to, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, troleandomycin, or atazanavir, a dose reduction should be considered in the presence of severe adverse events (see *Drug Interactions* section).

Dosing Considerations

Hepatic impairment: The safety and efficacy of TARCEVA has not been studied in patients with hepatic impairment. Erlotinib is eliminated by hepatic metabolism and biliary excretion. Therefore caution should be used when administering TARCEVA to patients with hepatic impairment. Dose reduction or interruption of TARCEVA should be considered if adverse reactions occur (see *Warnings and Precautions - Special Populations and Conditions - Patients with Hepatic Impairment*).

Renal impairment: The safety and efficacy of TARCEVA has not been studied in patients with renal impairment.

Geriatric use: No meaningful differences in safety or pharmacokinetics were observed between younger and older patients, therefore, no dosing adjustment is necessary (see *Indications and Clinical Use* section).

Missed Dose

A double-dose should not be administered to make up for forgotten individual doses.

OVERDOSAGE

Single oral doses of TARCEVA (erlotinib) 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 diarrhea, 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. For management of suspected drug overdose, contact your regional poison control centre.

ACTION AND CLINICAL PHARMACOLOGY

TARCEVA (erlotinib) is a Human Epidermal Growth Factor Receptor Type 1/Epidermal Growth Factor Receptor (HER1/EGFR) tyrosine kinase inhibitor.

Mode of Action: The mechanism of clinical antitumour action of erlotinib is not fully characterized. Erlotinib potently inhibits the intracellular phosphorylation of HER1/EGFR. HER1/EGFR is expressed on the cell surface of normal cells and cancer cells. Specificity of

erlotinib inhibition on other tyrosine kinase receptors of the ErbB family has not been characterized.

Pharmacokinetics

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 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 with [¹⁴C] labeled erlotinib in athymic nude mice with HN5 tumour xenografts have shown rapid and extensive tissue distribution with maximum concentrations of radiolabeled drug (approximately 73% of that in plasma) observed at 1 hour. Higher radioactivity exposure (4 - 8 fold as measured in other peripheral tissues) was observed in kidney and liver in these studies.

Metabolism: Erlotinib is metabolized in the liver by the hepatic cytochromes in humans, primarily CYP3A4 and to a lesser extent by CYP1A2, and the pulmonary isoform CYP1A1. *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 are present in plasma at levels that are <10% of erlotinib and display similar pharmacokinetics as erlotinib. The metabolites and trace amounts of erlotinib are excreted predominantly via the feces (>90%), with renal elimination accounting for only a small amount of an oral dose.

Excretion:

Clearance:

A population pharmacokinetic analysis in 591 patients receiving single agent TARCEVA shows a mean apparent clearance of 4.47 L/hour with a median half-life of 36.2 hours. Therefore, the time to reach steady state plasma concentration would be expected to occur in approximately 7-8

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

Patient factors, which correlate with erlotinib pharmacokinetics, are serum total bilirubin, AAG concentrations and current smoking. Increased serum concentrations of total bilirubin and AAG concentrations were associated with a slower rate of erlotinib clearance. Smokers had a 24% higher rate of erlotinib clearance.

Exposure:

Following a 150 mg oral dose of TARCEVA, at steady state, the median time to reach maximum plasma concentrations is approximately 4.0 hours with median maximum plasma concentrations achieved of 1,995 ng/mL. Prior to the next dose at 24 hours, the median minimum plasma concentrations are 1,238 ng/mL. Median AUC achieved during the dosing interval at steady state are 41,300 ng·hr/mL.

Special Populations and Conditions

Hepatic impairment: Erlotinib is mainly cleared by the liver. However, no data are currently available regarding the influence of hepatic metastases and/or hepatic dysfunction on the pharmacokinetics of erlotinib (see *Warnings and Precautions*; and *Dosage and Administration – Dosing Considerations*).

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

STORAGE AND STABILITY

Store TARCEVA (erlotinib) between 15 - 30°C. Do not use after the expiry date stated on the carton.

SPECIAL HANDLING INSTRUCTIONS

Keep out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TARCEVA (erlotinib) is available in 25 mg, 100 mg or 150 mg film-coated tablets.

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

Tablet core :

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

Tablet coat :

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

Description of film-coated tablets:

- White to yellowish, round, biconvex tablets with ‘Tarceva 25’ and logo printed in brownish yellow on one side.
- White to yellowish, round, biconvex tablets with ‘Tarceva 100’ and logo printed in grey on one side.
- White to yellowish, round, biconvex tablets with ‘Tarceva 150’ and logo printed in brown on one side.

Packaging: PVC blisters sealed with aluminum foil containing 10 tablets. Three (3) blisters of 10 tablets/carton.