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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-743

Approved Labeling

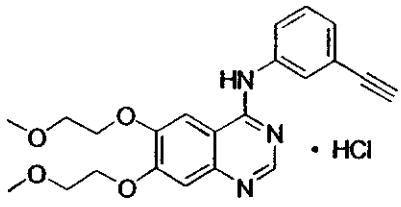
PACKAGE INSERT

TARCEVA™
(erlotinib)
Tablets

RX Only

DESCRIPTION

TARCEVA (erlotinib) is a Human Epidermal Growth Factor Receptor Type 1/Epidermal Growth Factor Receptor (HER1/EGFR) tyrosine kinase inhibitor. Erlotinib is a quinazolinamine with the chemical name N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine. TARCEVA contains erlotinib as the hydrochloride salt which has the following structural formula:



Erlotinib hydrochloride has the molecular formula $C_{22}H_{23}N_3O_4.HCl$ and a molecular weight of 429.90. The molecule has a pK_a of 5.42 at 25°C. Erlotinib hydrochloride is very slightly 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 of less than 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.

TARCEVA tablets are available in three dosage strengths containing erlotinib hydrochloride (27.3 mg, 109.3 mg and 163.9 mg) equivalent to 25 mg, 100 mg and 150 mg erlotinib and the following inactive ingredients: lactose monohydrate, hypromellose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate and titanium dioxide. The tablets also contain trace amounts of color additives, including FD&C Yellow #6 (25 mg only) for product identification.

CLINICAL PHARMACOLOGY

Mechanism of Action and Pharmacodynamics

The mechanism of clinical antitumor action of erlotinib is not fully characterized. Erlotinib inhibits the intracellular phosphorylation of tyrosine kinase associated with the epidermal growth factor receptor (EGFR). Specificity of inhibition with regard to other tyrosine kinase receptors has not been fully characterized. EGFR is expressed on the cell surface of normal cells and cancer cells.

Pharmacokinetics

Erlotinib is about 60% absorbed after oral administration and its bioavailability is substantially increased by food to almost 100%. Its half-life is about 36 hours and it is cleared predominantly by CYP3A4 metabolism.

Absorption and Distribution

Bioavailability of erlotinib following a 150 mg oral dose of TARCEVA is about 60% and peak plasma levels occur 4 hrs after dosing. Food increases bioavailability substantially, to almost 100%.

Following absorption, erlotinib is approximately 93% protein bound to albumin and alpha-1 acid glycoprotein (AAG). Erlotinib has an apparent volume of distribution of 232 liters.

Metabolism and Elimination

In vitro assays of cytochrome P450 metabolism showed that erlotinib is metabolized primarily by CYP3A4 and to a lesser extent by CYP1A2, and the extrahepatic isoform CYP1A1. Following a 100 mg oral dose, 91% of the dose was recovered: 83% in feces (1% of the dose as intact parent) and 8% in urine (0.3% of the dose as intact parent).

A population pharmacokinetic analysis in 591 patients receiving single-agent TARCEVA showed a median half-life of 36.2 hours. Time to reach steady state plasma concentration would therefore be 7 - 8 days. No significant relationships of clearance to patient age, body weight or gender were observed. Smokers had a 24% higher rate of erlotinib clearance.

Special Populations

Patients with Hepatic Impairment

Erlotinib is cleared predominantly by the liver. No data are currently available regarding the influence of hepatic dysfunction and/or hepatic metastases on the pharmacokinetics of erlotinib (see **PRECAUTIONS - Patients with Hepatic Impairment, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION - Dose Modifications** sections).

Patients with Renal Impairment

Less than 9% of a single dose is excreted in the urine. No clinical studies have been conducted in patients with compromised renal function.

Interactions

Erlotinib is metabolized predominantly by CYP3A4, and inhibitors of CYP3A4 would be expected to increase exposure. Co-treatment with the potent CYP3A4 inhibitor ketoconazole increased erlotinib AUC by 2/3 (see **PRECAUTIONS - Drug Interactions** and **DOSAGE AND ADMINISTRATION - Dose Modifications** sections).

Pre- or co-treatment with the CYP3A4 inducer rifampicin increased erlotinib clearance by 3-fold and reduced AUC by 2/3 (see **PRECAUTIONS - Drug Interactions** and **DOSAGE AND ADMINISTRATION - Dose Modifications** sections).

CLINICAL STUDIES

TARCEVA as Monotherapy in Non-Small Cell Lung Cancer (NSCLC)

The efficacy and safety of TARCEVA was assessed in a randomized, double blind, placebo-controlled trial in 731 patients with locally advanced or metastatic NSCLC after failure of at least one chemotherapy regimen. Patients were randomized 2:1 to receive TARCEVA 150 mg or placebo (488 Tarceva, 243 placebo) 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. The study was conducted in

17 countries. About 1/3 of the patients (238) had EGFR expression status characterized.

Table 1 summarizes the demographic and disease characteristics of the study population. Demographic characteristics were well balanced between the two treatment groups. About two-thirds of the patients were male. Approximately one-fourth had a baseline ECOG performance status (PS) of 2, and 9% had a baseline ECOG PS of 3. Fifty percent of the patients had received only one prior regimen of chemotherapy. About three quarters of these patients were known to have smoked at some time.

Table 1: Demographic and Disease Characteristics

	TARCEVA (N = 488)		Placebo (N = 243)	
Characteristics	**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)
Race				
Caucasian	379	(78)	188	(77)
Black	18	(4)	12	(5)
Asian	63	(13)	28	(12)
Other	28	(6)	15	(6)
ECOG Performance Status at Baseline*				
0	64	(13)	34	(14)
1	256	(52)	132	(54)
2	126	(26)	56	(23)
3	42	(9)	21	(9)
Weight Loss in Previous 6 Months				
< 5%	320	(66)	166	(68)
5 – 10%	96	(20)	36	(15)

	TARCEVA (N = 488)		Placebo (N = 243)	
Characteristics	**N**	**(%)**	**N**	**(%)**
> 10%	52	(11)	29	(12)
Unknown	20	(4)	12	(5)
Smoking History				
Never Smoked	104	(21)	42	(17)
Current or Ex-smoker	358	(73)	187	(77)
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)
Time from Initial Diagnosis to Randomization (Months)				
<6	63	(13)	34	(14)
6 – 12	157	(32)	85	(35)
>12	268	(55)	124	(51)
Best Response to Prior Therapy at Baseline*				
CR/PR	196	(40)	96	(40)
PD	101	(21)	51	(21)
SD	191	(39)	96	(40)
Number of Prior Regimens at Baseline*				
1	243	(50)	121	(50)
2	238	(49)	119	(49)
3	7	(1)	3	(1)
Exposure to Prior Platinum at Baseline*				
Yes	454	(93)	224	(92)
No	34	(7)	19	(8)

* Stratification factor as documented at baseline; distribution differs slightly from values reported at time of randomization.

The results of the study are shown in Table 2.

Table 2: Efficacy Results

	Tarceva	Placebo	Hazard Ratio (1)	95% CI	p-value
Survival	Median 6.7 mo	Median 4.7 mo	0.73	0.61 – 0.86	<0.001 (2)
1-year Survival	31.2%	21.5%			
Progression-Free Survival	Median 9.9 wk	Median 7.9 wk	0.59	0.50 – 0.70	<0.001 (2)
Tumor Response (CR+PR)	8.9%	0.9%			<0.001 (3)
Response Duration	Median 34.3 wk	Median 15.9 wk			

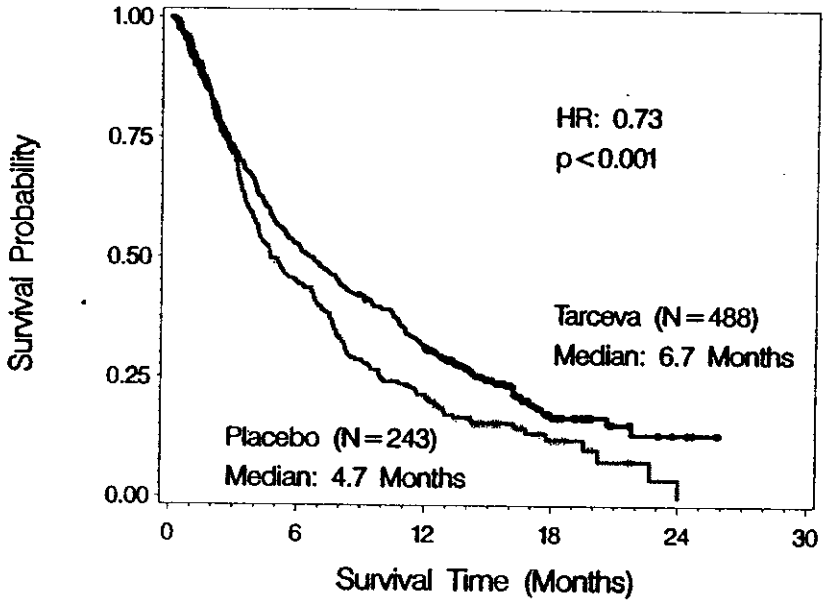
(1) Cox regression model with the following covariates: ECOG performance status, number of prior regimens, prior platinum, best response to prior chemotherapy.

(2) Two-sided Log-Rank test stratified by ECOG performance status, number of prior regimens, prior platinum, best response to prior chemotherapy.

(3) Two-sided Fisher's exact test

Survival was evaluated in the intent-to-treat population. Figure 1 depicts the Kaplan-Meier curves for overall survival. The primary survival and PFS analyses were two-sided Log-Rank tests stratified by ECOG performance status, number of prior regimens, prior platinum, best response to prior chemotherapy.

Figure 1: Kaplan–Meier Curve for Overall Survival of Patients by Treatment Group

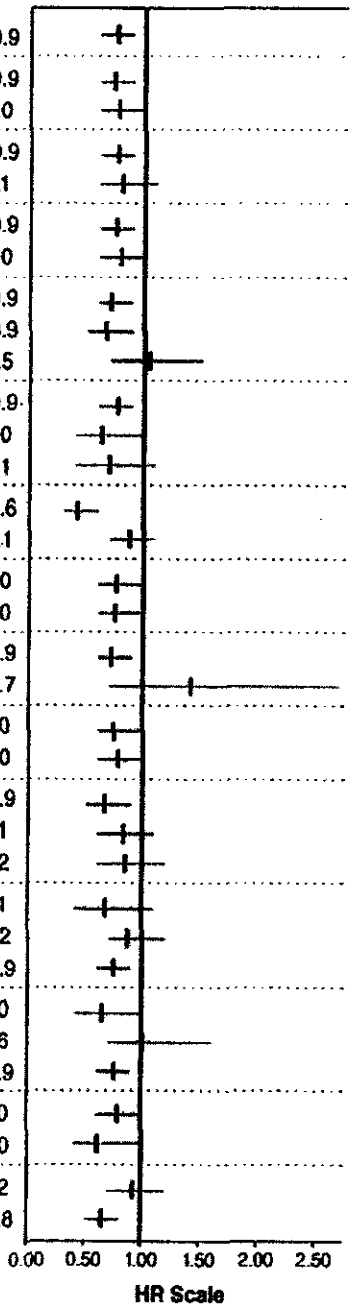


Note: HR is from Cox regression model with the following covariates: ECOG performance status, number of prior regimens, prior platinum, best response to prior chemotherapy. P-value is from two-sided Log-Rank test stratified by ECOG performance status, number of prior regimens, prior platinum, best response to prior chemotherapy.

A series of subsets of patients were examined in exploratory univariate analyses. The results of these analyses are shown in Figure 2.The effect of TARCEVA on survival was similar across most subsets. An apparently larger effect, however, was observed in two subsets: patients with EGFR positive tumors (HR = 0.65) and patients who never smoked (HR = 0.42). These subsets are considered further below.

Figure 2: Survival Hazard Ratio (HR) (Tarceva : Placebo) in Subgroups According to Pretreatment Characteristics

Factors	N	HR	95% CI
Tarceva : Placebo	731	0.76	0.6 – 0.9
Performance Status 0–1	486	0.73	0.6 – 0.9
Performance Status 2–3	245	0.77	0.6 – 1.0
Male	475	0.76	0.6 – 0.9
Female	256	0.80	0.6 – 1.1
Age <65	452	0.75	0.6 – 0.9
Age ≥65	279	0.79	0.6 – 1.0
Adeno Ca	365	0.71	0.6 – 0.9
Squamous Cell Ca	222	0.67	0.5 – 0.9
Other Histology	144	1.04	0.7 – 1.5
Prior Weight Loss <5%	486	0.77	0.6 – 0.9
Prior Weight Loss 5–10%	132	0.63	0.4 – 1.0
Prior Weight Loss >10%	81	0.70	0.4 – 1.1
Never Smoked	146	0.42	0.3 – 0.6
Current/Ex-Smoker	545	0.87	0.7 – 1.1
One Prior Regimen	364	0.76	0.6 – 1.0
Two+ Prior Regimens	367	0.75	0.6 – 1.0
Prior Platinum	678	0.72	0.6 – 0.9
No Prior Platinum	53	1.41	0.7 – 2.7
Prior Taxane	267	0.74	0.6 – 1.0
No Prior Taxane	464	0.78	0.6 – 1.0
Best Prior Response: CR/PR	292	0.67	0.5 – 0.9
Best Prior Response: SD	287	0.83	0.6 – 1.1
Best Prior Response: PD	152	0.85	0.6 – 1.2
<6 mos Since Diagnosis	97	0.68	0.4 – 1.1
6–12 mos Since Diagnosis	242	0.87	0.7 – 1.2
>12 mos Since Diagnosis	392	0.75	0.6 – 0.9
EGFR Positive	127	0.65	0.4 – 1.0
EGFR Negative	111	1.01	0.7 – 1.6
EGFR Unmeasured	493	0.76	0.6 – 0.9
Caucasian	567	0.79	0.6 – 1.0
Asian	91	0.61	0.4 – 1.0
Stage IV at Diagnosis	329	0.92	0.7 – 1.2
Stage <IV at Diagnosis	402	0.65	0.5 – 0.8



Note: Depicted are the univariate hazard ratio (HR) for death in the TARCEVA patients relative to the placebo patients, the 95% confidence interval (CI) for the

HR, and the sample size (N) in each subgroup. The hash mark on the horizontal bar represents the HR, and the length of the horizontal bar represents the 95% confidence interval. A hash mark to the left of the vertical line corresponds to a HR that is less than 1.00, which indicates that survival is better in the TARCEVA arm compared with the placebo arm in that subgroup.

Relation of Results to EGFR Protein Expression Status (as Determined by Immunohistochemistry)

Analysis of the impact of EGFR expression status on the treatment effect on clinical outcome is limited because EGFR status is known for only 238 study patients (33%). EGFR status was ascertained for patients who already had tissue samples prior to study enrollment. However, the survival in the EGFR tested population, and the effect of TARCEVA were almost identical to that in the entire study population, suggesting that the tested population was a representative sample. A positive EGFR expression status was defined as having at least 10% of cells staining for EGFR in contrast to the 1% cut-off specified in the DAKO EGFR pharmDx™ kit instructions. The use of the pharmDx kit has not been validated for use in non-small cell lung cancer.

TARCEVA prolonged survival in the EGFR positive subgroup (N = 127; HR = 0.65; 95% CI = 0.43 – 0.97)(Figure 3) and the subgroup whose EGFR status was unmeasured (N = 493; HR = 0.76; 95% CI = 0.61 – 0.93)(Figure 5), but did not appear to have an effect on survival in the EGFR negative subgroup (N = 111; HR = 1.01; 95% CI = 0.65 – 1.57)(Figure 4). However, the confidence intervals for the EGFR positive, negative and unmeasured subgroups are wide and overlap, so that a survival benefit due to TARCEVA in the EGFR negative subgroup cannot be excluded.

For the subgroup of patients who never smoked, EGFR status also appeared to be predictive of TARCEVA survival benefit. Patients who never smoked and were EGFR positive had a large TARCEVA survival benefit (N = 30; HR = 0.27; 95% CI = 0.11 – 0.67). There were too few EGFR negative patients who never smoked to reach a conclusion.

Tumor responses were observed in all EGFR subgroups: 11.6% in the EGFR positive subgroup, 9.5% in the EGFR unmeasured subgroup and 3.2% in the EGFR negative

subgroup. An improvement in progression free survival was demonstrated in the EGFR positive subgroup (HR = 0.49; 95% CI = 0.33 – 0.72), the EGFR unmeasured subgroup (HR = 0.56; 95% CI = 0.46 – 0.70), and less certain in the EGFR negative subgroup (HR = 0.91; 95% CI = 0.59 – 1.39).

Figure 3: Survival in EGFR Positive Patients

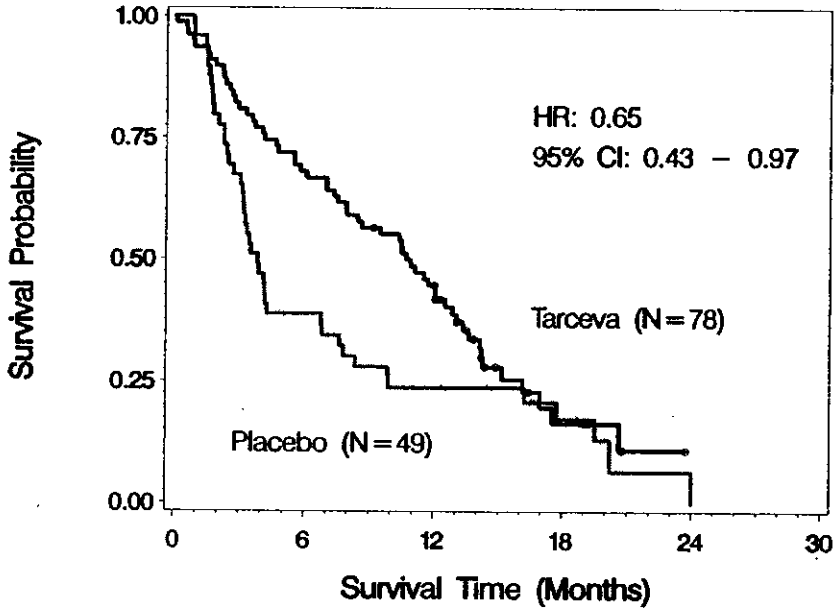


Figure 4: Survival in EGFR Negative Patients

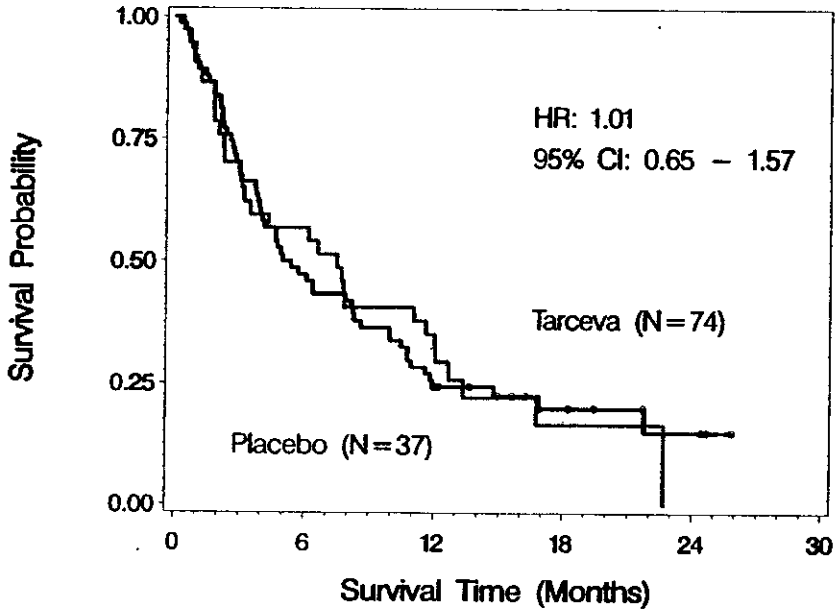
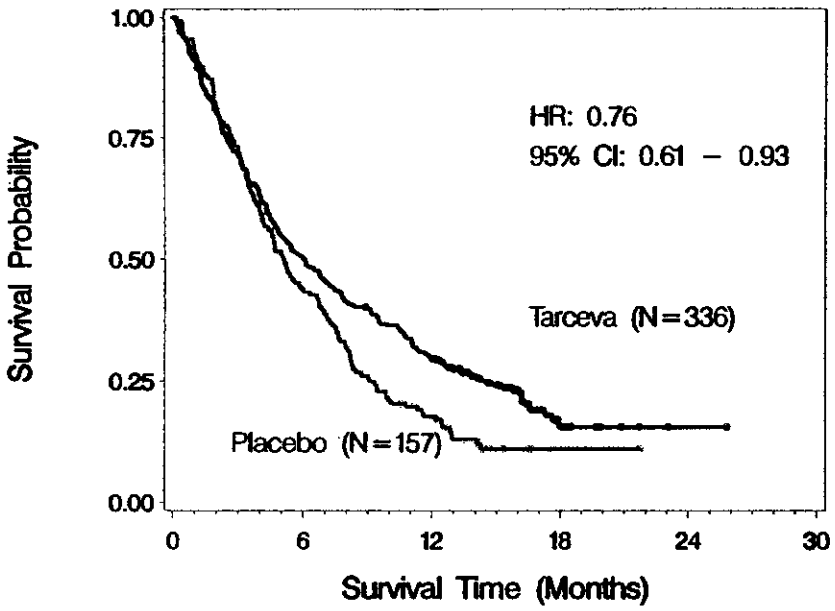


Figure 5: Survival in EGFR Unmeasured Patients



TARCEVA Administered Concurrently with Chemotherapy in NSCLC

Results from two, multicenter, placebo-controlled, randomized, trials in over 1000 patients conducted in first-line patients with locally advanced or metastatic NSCLC showed no clinical benefit with the concurrent administration of TARCEVA with platinum-based chemotherapy [carboplatin and paclitaxel (TARCEVA, N = 526) or gemcitabine and cisplatin (TARCEVA, N = 580)].

INDICATIONS AND USAGE

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

Results from two, multicenter, placebo-controlled, randomized, Phase 3 trials conducted in first-line patients with locally advanced or metastatic NSCLC showed no clinical benefit with the concurrent administration of TARCEVA with platinum-based chemotherapy [carboplatin and paclitaxel or gemcitabine and cisplatin] and its use is not recommended in that setting.

CONTRAINDICATIONS

None.

WARNINGS

Pulmonary Toxicity

There have been infrequent reports of serious Interstitial Lung Disease (ILD), including fatalities, in patients receiving TARCEVA for treatment of NSCLC or other advanced solid tumors. In the randomized single-agent study (see **CLINICAL STUDIES** section), the incidence of ILD (0.8%) was the same in both the placebo and TARCEVA groups. 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 pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome and lung infiltration. Symptoms started from 5 days to more than 9 months (median 47 days) after initiating TARCEVA therapy. Most of the cases were associated with confounding or contributing factors such as concomitant/prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections.

In the event of acute onset of new 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 instituted as necessary (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION - Dose Modifications** sections).

Pregnancy Category D

Erlotinib has been shown to cause maternal toxicity with associated embryo/fetal lethality and abortion in rabbits when given at doses that result in plasma drug concentrations of approximately 3 times those in humans (AUCs at 150 mg daily dose). When given during the period of organogenesis to achieve plasma drug concentrations approximately equal to those in humans, based on AUC, there was no increased incidence of embryo/fetal lethality or abortion in rabbits or rats. However, female rats treated with 30 mg/m^2/day or 60 mg/m^2/day (0.3 or 0.7 times the clinical

dose, on a mg/m^2 basis) of erlotinib prior to mating through the first week of pregnancy had an increase in early resorptions which resulted in a decrease in the number of live fetuses.

No teratogenic effects were observed in rabbits or rats.

There are no adequate and well-controlled studies in pregnant women using TARCEVA. Women of childbearing potential should 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 should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

PRECAUTIONS

Drug Interactions

Co-treatment with the potent CYP3A4 inhibitor ketoconazole increases erlotinib AUC by 2/3. Caution should be used when administering or taking TARCEVA with ketoconazole and other strong CYP3A4 inhibitors such as atanazavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), and voriconazole (see **DOSAGE AND ADMINISTRATION - Dose Modifications** section).

Pre-treatment with the CYP3A4 inducer rifampicin decreased erlotinib AUC by about 2/3. Alternate treatments lacking CYP3A4 inducing activity should be considered. If an alternative treatment is unavailable, a TARCEVA dose greater than 150 mg should be considered. If the TARCEVA dose is adjusted upward, the dose will need to be reduced upon discontinuation of rifampicin or other inducers. Other CYP3A4 inducers include rifabutin, rifapentin, phenytoin, carbamazepine, phenobarbital and St. John's Wort (see **DOSAGE AND ADMINISTRATION - Dose Modifications** section).

Hepatotoxicity

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).

Patients with Hepatic Impairment

In vitro and *in vivo* evidence suggest that erlotinib is cleared primarily by the liver. Therefore, erlotinib exposure may be increased in patients with hepatic dysfunction (see **CLINICAL PHARMACOLOGY - Special Populations - Patients with Hepatic Impairment** and **DOSAGE AND ADMINISTRATION - Dose Modification** sections).

Elevated International Normalized Ratio and Potential Bleeding

International Normalized Ratio (INR) elevations, and infrequent reports of 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 (see **ADVERSE REACTIONS** section).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Erlotinib has not been tested for carcinogenicity.

Erlotinib 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 bone marrow micronucleus test and did not cause genetic damage. Erlotinib did not impair fertility in either male or female rats.

Pregnancy

Pregnancy Category D (see **WARNINGS** and **PRECAUTIONS - Information for Patients** sections).

Nursing Mothers

It is not known whether erlotinib is excreted in human milk. Because many drugs are excreted in human milk and because the effects of TARCEVA on infants have not been studied, women should be advised against breast-feeding while receiving TARCEVA therapy.

Pediatric Use

The safety and effectiveness of TARCEVA in pediatric patients have not been studied.

Geriatric Use

Of the total number of patients participating in the randomized trial, 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 **CLINICAL STUDIES** section). No meaningful differences in safety or pharmacokinetics were observed between younger and older patients. Therefore, no dosage adjustments are recommended in elderly patients.

Information for Patients

If the following signs or symptoms occur, patients should seek medical advice promptly (see **WARNINGS, ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION - Dose Modification** sections).

- Severe or persistent diarrhea, nausea, anorexia, or vomiting
- Onset or worsening of unexplained shortness of breath or cough
- Eye irritation

Women of childbearing potential should be advised to avoid becoming pregnant while taking TARCEVA (see **WARNINGS - Pregnancy Category D** section).

ADVERSE REACTIONS

Safety evaluation of TARCEVA is based on 856 cancer patients who received TARCEVA as monotherapy and 1228 patients who received TARCEVA concurrently with chemotherapy. Adverse events, regardless of causality, that occurred in at least 10% of patients treated with TARCEVA and at least 3% more often than in the placebo group in the randomized trial are summarized by NCI-CTC (version 2.0) Grade in Table 3.

There have been reports of serious ILD, including fatalities, in patients receiving TARCEVA for treatment of NSCLC or other advanced solid tumors (see **WARNINGS - Pulmonary Toxicity**, and **DOSAGE AND ADMINISTRATION - Dose Modifications** sections).

The most common adverse reactions in patients receiving TARCEVA were rash and diarrhea. Grade 3/4 rash and diarrhea occurred in 9% and 6%, respectively, in TARCEVA-treated patients. Rash and diarrhea each resulted in study discontinuation in 1% of TARCEVA-treated patients. Six percent and 1% of patients needed dose reduction for rash and diarrhea, respectively. The median time to onset of rash was 8 days, and the median time to onset of diarrhea was 12 days.

Table 3: Adverse Events Occurring in ≥10% of TARCEVA-treated Patients (2:1 Randomization of TARCEVA to Placebo)

	TARCEVA N = 485			Placebo N = 242		
NCI CTC Grade	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
MedDRA Preferred Term	**%**	**%**	**%**	**%**	**%**	**%**
Rash	75	8	<1	17	0	0
Diarrhea	54	6	<1	18	<1	0
Anorexia	52	8	1	38	5	<1
Fatigue	52	14	4	45	16	4
Dyspnea	41	17	11	35	15	11
Cough	33	4	0	29	2	0
Nausea	33	3	0	24	2	0
Infection	24	4	0	15	2	0
Vomiting	23	2	<1	19	2	0
Stomatitis	17	<1	0	3	0	0
Pruritus	13	<1	0	5	0	0
Dry skin	12	0	0	4	0	0
Conjunctivitis	12	<1	0	2	<1	0
Keratoconjunctivitis sicca	12	0	0	3	0	0
Abdominal pain	11	2	<1	7	1	<1

Liver function test abnormalities (including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin) have been observed. These elevations were mainly transient or associated with liver metastases. 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 - Dose Modification** section).

Infrequent cases of gastrointestinal bleeding have been reported in clinical studies, some associated with concomitant warfarin administration (see **PRECAUTIONS - Elevated International Normalized Ratio and Potential Bleeding** section) and some with concomitant NSAID administration.

NCI CTC grade 3 conjunctivitis and keratitis have been reported infrequently in patients receiving TARCEVA therapy. Corneal ulcerations may also occur (see **PRECAUTIONS - Information for Patients** section).

In general, no notable differences in the safety of TARCEVA could be discerned between females or males and between patients younger or older than the age of 65 years. The safety of TARCEVA appears similar in Caucasian and Asian patients (see **PRECAUTIONS - Geriatric Use** section).

OVERDOSAGE

Single oral doses of TARCEVA up to 1,000 mg in healthy subjects, and up to 1,600 mg 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, an unacceptable incidence of severe adverse events, such as diarrhea, rash, and 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 instituted.

DOSAGE AND ADMINISTRATION

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

Dose Modifications

In patients who develop an acute onset of new or progressive pulmonary symptoms, such as dyspnea, cough or fever, treatment with TARCEVA should be interrupted pending diagnostic evaluation. If ILD is diagnosed, TARCEVA should be

discontinued and appropriate treatment instituted as necessary (see **WARNINGS – Pulmonary Toxicity** section).

Diarrhea can usually be managed with loperamide. Patients with severe diarrhea who are unresponsive to loperamide or who become dehydrated may require dose reduction or temporary interruption of therapy. Patients with severe skin reactions may also require dose reduction or temporary interruption of therapy.

When dose reduction is necessary, the TARCEVA dose should be reduced in 50 mg decrements.

In patients who are being concomitantly treated with a strong CYP3A4 inhibitor such as atanazavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), or voriconazole, a dose reduction should be considered should severe adverse reactions occur.

Pre-treatment with the CYP3A4 inducer rifampicin decreased erlotinib AUC by about 2/3. Alternate treatments lacking CYP3A4 inducing activity should be considered. If an alternative treatment is unavailable, a TARCEVA dose greater than 150 mg should be considered. If the TARCEVA dose is adjusted upward, the dose will need to be reduced upon discontinuation of rifampicin or other inducers. Other CYP3A4 inducers include rifabutin, rifapentin, phenytoin, carbamazepine, phenobarbital and St. John's Wort. These too should be avoided if possible (see **PRECAUTIONS - Drug Interactions** section).

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 should severe adverse reactions occur (see **CLINICAL PHARMACOLOGY - Special Populations – Patients With Hepatic Impairment, PRECAUTIONS - Patients With Hepatic Impairment,** and **ADVERSE REACTIONS** sections).

HOW SUPPLIED

The 25 mg, 100 mg and 150 mg strengths are supplied as white film-coated tablets for daily oral administration.

TARCEVA™ (erlotinib) Tablets, 25 mg: Round, biconvex face and straight sides, white film-coated, printed in orange with a "T" and "25" on one side and plain on the other side. Supplied in bottles of 30 tablets (NDC 50242-062-01).

TARCEVA™ (erlotinib) Tablets, 100 mg: Round, biconvex face and straight sides, white film-coated, printed in gray with "T" and "100" on one side and plain on the other side. Supplied in bottles of 30 tablets (NDC 50242-063-01).

TARCEVA™ (erlotinib) Tablets, 150 mg: Round, biconvex face and straight sides, white film-coated, printed in maroon with "T" and "150" on one side and plain on the other side. Supplied in bottles of 30 tablets (NDC 50242-064-01).

STORAGE

Store at 25°C (77°F); excursions permitted to 15° – 30°C (59° – 86°F). See USP Controlled Room Temperature.

Manufactured for:

OSI Pharmaceuticals Inc., Melville, NY 11747

Manufactured by:

Schwarz Pharma Manufacturing, Seymour, IN 47274

Distributed by:

Genentech Inc., 1 DNA Way, South San Francisco, CA 94080-4990

For further information please call 1-877-TARCEVA (1-877-827-2382).

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