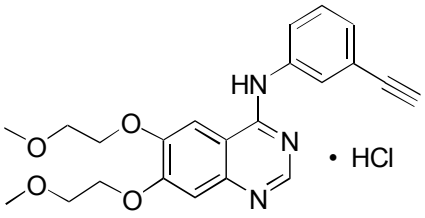
PACKAGE INSERT

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.

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