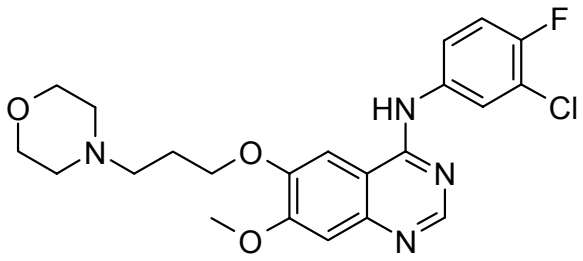
IRESSA®
(gefitinib tablets)

FOR ONCOLOGY USE ONLY

DESCRIPTION

IRESSA® (gefitinib tablets) contain 250 mg of gefitinib and are available as brown film-coated tablets for daily oral administration.

Gefitinib is an anilinoquinazoline with the chemical name 4-Quinazolinamine, *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-4-morpholin) propoxy] and the following structural formula:



It has the molecular formula $C_{22}H_{24}ClFN_4O_3$, a relative molecular mass of 446.9 and is a white-colored powder. Gefitinib is a free base. The molecule has pK_as of 5.4 and 7.2 and therefore ionizes progressively in solution as the pH falls. Gefitinib can be defined as sparingly soluble at pH 1, but is practically insoluble above pH 7, with the solubility dropping sharply between pH 4 and pH 6. In non-aqueous solvents, gefitinib is freely soluble in glacial acetic acid and dimethylsulphoxide, soluble in pyridine, sparingly soluble in tetrahydrofuran, and slightly soluble in methanol, ethanol (99.5%), ethyl acetate, propan-2-ol and acetonitrile.

The inactive ingredients of IRESSA tablets are: **Tablet core:** Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate and magnesium stearate. **Coating:** hypromellose, polyethylene glycol 300, titanium dioxide, red ferric oxide and yellow ferric oxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of the clinical antitumor action of gefitinib is not fully characterized. Gefitinib inhibits the intracellular phosphorylation of numerous tyrosine kinases associated with transmembrane cell surface receptors, including the tyrosine kinases associated with the epidermal growth factor receptor (EGFR-TK). EGFR is expressed on the cell surface of many normal cells and cancer cells. No clinical studies have been performed that demonstrate a correlation between EGFR receptor expression and response to gefitinib.

Pharmacokinetics

Gefitinib is absorbed slowly after oral administration with mean bioavailability of 60%. Elimination is by metabolism (primarily CYP3A4) and excretion in feces. The elimination half-life is about 48 hours. Daily oral administration of gefitinib to cancer patients resulted in a 2-fold accumulation compared to single dose administration. Steady state plasma concentrations are achieved within 10 days.

Absorption and Distribution

Gefitinib is slowly absorbed, with peak plasma levels occurring 3-7 hours after dosing and mean oral bioavailability of 60%. Bioavailability is not significantly altered by food. Gefitinib is extensively distributed throughout the body with a mean steady state volume of distribution of 1400 L following intravenous administration. *In vitro* binding of gefitinib to human plasma proteins (serum albumin and α1-acid glycoprotein) is 90% and is independent of drug concentrations.

Metabolism and Elimination

Gefitinib undergoes extensive hepatic metabolism in humans, predominantly by CYP3A4. Three sites of biotransformation have been identified: metabolism of the N-propoxymorpholino-group, demethylation of the methoxy-substituent on the quinazoline, and oxidative defluorination of the halogenated phenyl group.

Five metabolites were identified in human plasma. Only O-desmethyl gefitinib has exposure comparable to gefitinib. Although this metabolite has similar EGFR-TK activity to gefitinib in the isolated enzyme assay, it had only 1/14 of the potency of gefitinib in one of the cell-based assays.

Gefitinib is cleared primarily by the liver, with total plasma clearance and elimination half-life values of 595 mL/min and 48 hours, respectively, after intravenous administration. Excretion is predominantly via the feces (86%), with renal elimination of drug and metabolites accounting for less than 4% of the administered dose.

Special Populations

In population based data analyses, no relationships were identified between predicted steady state trough concentration and patient age, body weight, gender, ethnicity or creatinine clearance.

Pediatric:

There are no pharmacokinetic data in pediatric patients.

Hepatic Impairment:

The influence of hepatic metastases with elevation of serum aspartate aminotransferase (AST/SGOT), alkaline phosphatase, and bilirubin has been evaluated in patients with normal (14 patients), moderately elevated (13 patients) and severely elevated (4 patients) levels of one or more of these biochemical parameters. Patients with moderately and severely elevated biochemical liver abnormalities had gefitinib pharmacokinetics similar to individuals without liver abnormalities (see **PRECAUTIONS** section).

Renal Impairment:

No clinical studies were conducted with IRESSA in patients with severely compromised renal function (see **PRECAUTIONS** section). Gefitinib and its metabolites are not significantly excreted via the kidney (<4%).

Drug-Drug Interactions:

In human liver microsome studies, gefitinib had no inhibitory effect on CYP1A2, CYP2C9, and CYP3A4 activities at concentrations ranging from 2-5000 ng/mL. At the highest concentration studied (5000 ng/mL), gefitinib inhibited CYP2C19 by 24% and CYP2D6 by 43%. Exposure to metoprolol, a substrate of CYP2D6, was increased by 30% when it was given in combination with gefitinib (500 mg daily for 28 days) in patients with solid tumors.

Rifampicin, an inducer of CYP3A4, reduced mean AUC of gefitinib by 85% in healthy male volunteers (see **PRECAUTIONS-Drug Interactions** and **DOSAGE AND ADMINISTRATION-Dosage Adjustment** sections).

Concomitant administration of itraconazole (200 mg QD for 12 days), an inhibitor of CYP3A4, with gefitinib (250 mg single dose) to healthy male volunteers, increased mean gefitinib AUC by 88% (see **PRECAUTIONS-Drug Interactions** section).

Co-administration of high doses of ranitidine with sodium bicarbonate (to maintain the gastric pH above pH 5.0) reduced mean gefitinib AUC by 44% (See **PRECAUTIONS-Drug Interactions** section).

International Normalized Ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin while on IRESSA therapy. Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR (see **PRECAUTIONS-Drug Interactions** and **ADVERSE REACTIONS** sections).

Clinical Studies

Non-Small Cell Lung Cancer (NSCLC): Refractory Disease Tumor Response Study - A multicenter clinical trial in the United States evaluated the tumor response rate of IRESSA 250 and 500 mg/day in patients with advanced non-small cell lung cancer whose disease had progressed after at least two prior chemotherapy regimens including a platinum drug and docetaxel. IRESSA was taken once daily at approximately the same time each day.

Two hundred and sixteen patients received IRESSA, 102 (47%) and 114 (53%) receiving 250 mg and 500 mg daily doses, respectively. Study patient demographics and disease characteristics are summarized in Table 1. Forty-one percent of the patients had received two prior treatment regimens, 33% three prior treatment regimens, and 25% four or more prior treatment regimens. Effectiveness of

IRESSA as third line therapy was determined in the 142 evaluable patients with documented disease progression on platinum and docetaxel therapies or who had had unacceptable toxicity on these agents.

Table 1: Demographic and Disease Characteristics

	IRESSA Dose	
Characteristic	**250 mg/day N = 66 (%)**	**500 mg/day N = 76 (%)**
Age Group		
18 – 64 years	43 (65)	43 (57)
64 – 74 years	19 (29)	30 (39)
75 years and above	4 (6)	3 (4)
Sex		
Male	38 (58)	41 (54)
Female	28 (42)	35 (46)
Race		
White	61 (92)	68 (89)
Black	1 (2)	2 (3)
Asian/Oriental	1 (2)	2 (3)
Hispanic	0 (0)	3 (4)
Other	3 (5)	1 (1)
Smoking History		
Yes (Previous or current Smoker)	45 (68)	62 (82)
No (Never Smoked)	21 (32)	14 (18)
Baseline WHO Performance Status		
0	14 (21)	9 (12)
1	36 (55)	53 (70)
2	15 (23)	14 (18)
Not recorded	1 (2)	0 (0)
Tumor Histology		
Squamous	9 (14)	11 (14)
Adenocarcinoma	47 (71)	50 (66)
Undifferentiated	6 (9)	4 (5)
Large Cell	1 (2)	2 (3)
Squamous & Adenocarcinoma	3 (5)	7 (9)
Not Recorded	0 (0)	2 (3)
Current Disease Status		
Locally Advanced	11 (17)	5 (7)
Metastatic	55 (83)	71 (93)

Table 2 shows tumor response rates and response duration. The overall response rate for the 250 and 500 mg doses combined was 10.6% (95% CI: 6%, 16.8%). Response rates appeared to be highly variable in subgroups of the treated population: 5.1% (4/79) in males, 17.5% (11/63) in females, 4.6% (5/108) in previous or current smokers, 29.4% (10/34) in nonsmokers, 12.4% (12/97) with adenocarcinoma histology, and 6.7% (3/45) with other NSCLC histologies. Similar differences were seen in a multinational study in patients who had received 1 or 2 prior chemotherapy regimens, at least 1 of which was platinum-based. In responders, the median time from diagnosis to study randomization was 16.7 months (range 8 to 34 months).

Table 2: Efficacy Results

	Efficacy Population		
	250 mg (N=66)	500 mg (N=76)	Combined (N=142)
Objective Tumor Response Rate (%)	13.6	7.9	10.6
95% CI	6.4– 24.3	3.0 – 16.4	6.0 – 16.8
Median Duration of Objective Response (months)	8.9	4.5	7.0
Range (months)	4.6 – 18.6+	4.4 – 7.6	4.4 – 18.6+
+=data are ongoing			

Non-Small Cell Lung Cancer (NSCLC): Refractory Disease Survival Study

A double-blind, placebo-controlled parallel-group trial randomized 1692 patients with advanced NSCLC to receive either IRESSA 250 mg daily plus Best Supportive Care or placebo plus Best Supportive Care. Patients had received 1 or 2 prior chemotherapy regimens and had progressed while receiving or within 90 days of the last dose of chemotherapy or were intolerant to the most recent prior chemotherapy regimen. The two treatment arms were well balanced for demographic and disease-related patient characteristics. The primary endpoint of the study was survival. IRESSA did not significantly prolong survival (stratified log rank HR 0.89, P=0.11, Median 5.6 vs 5.1 months for IRESSA and placebo respectively).

Non-Small Cell Lung Cancer (NSCLC); Studies of First-line Treatment in Combination with Chemotherapy - Two large trials were conducted in chemotherapy-naïve patients with stage III and IV non-small cell lung cancer. Two thousand one hundred thirty patients were randomized to receive IRESSA 250 mg daily, IRESSA 500 mg daily, or placebo in combination with platinum-based chemotherapy regimens. The chemotherapies given in these first-line trials were gemcitabine and cis-platinum (N=1093) or carboplatin and paclitaxel (N=1037). The addition of IRESSA did not demonstrate any increase, or trend toward such an increase, in tumor response rates, time to progression, or overall survival.

INDICATIONS AND USAGE

IRESSA is indicated as monotherapy for the continued treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies who are benefiting or have benefited from IRESSA.

In light of positive survival data with other agents including another oral EGFR inhibitor, physicians should use other treatment options in advanced non-small cell lung cancer patient populations who have received one or two prior chemotherapy regimens and are refractory or intolerant to their most recent regimen.

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