

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GEFITINIB TABLETS safely and effectively. See full prescribing information for GEFITINIB TABLETS.

GEFITINIB tablets, for oral use

Initial U.S. Approval: 2015

### INDICATIONS AND USAGE

Gefitinib tablets are a tyrosine kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. (1)

Limitation of Use: Safety and efficacy of gefitinib tablets have not been established in patients whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations. (1)

### DOSAGE AND ADMINISTRATION

Recommended dose is 250 mg orally, once daily with or without food. (2.2)

### DOSAGE FORMS AND STRENGTHS

Tablets: 250 mg. (3)

### CONTRAINDICATIONS

None. (4)

### WARNINGS AND PRECAUTIONS

- Interstitial lung disease (ILD): ILD occurred in patients taking gefitinib tablets. Withhold gefitinib tablets for worsening of respiratory symptoms. Discontinue gefitinib tablets if ILD is confirmed. (2.4, 5.1)
- Hepatotoxicity: Obtain periodic liver function testing. Withhold gefitinib tablets for Grade 2 or higher for ALT and/or AST elevations. Discontinue for severe hepatic impairment. (2.4, 5.2)
- Gastrointestinal perforation: Discontinue gefitinib tablets for gastrointestinal perforation. (2.4, 5.3)
- Diarrhea: Withhold gefitinib tablets for Grade 3 or higher diarrhea. (2.4, 5.4)

- Ocular Disorders including Keratitis: Withhold gefitinib tablets for signs and symptoms of severe or worsening ocular disorders including keratitis. Discontinue for persistent ulcerative keratitis. (2.4, 5.5)
- Bullous and Exfoliative Skin Disorders: Withhold gefitinib tablets for Grade 3 or higher skin reactions or exfoliative conditions. (2.4, 5.6)
- Embryo-fetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.7, 8.1, 8.3)

### ADVERSE REACTIONS

The most commonly reported adverse drug reactions (ADRs), reported in more than 20% of the patients and greater than placebo were skin reactions and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Apotex Inc. at 1-800-706-5575 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- CYP3A4 Inducer: Increase gefitinib tablets to 500 mg daily in patients receiving a strong CYP3A4 inducer. (2.4, 7.1)
- CYP3A4 Inhibitor: Monitor adverse reactions if concomitant use with gefitinib tablets. (7.1)
- Drugs Affecting Gastric pH: Avoid concomitant use of gefitinib tablets with proton pump inhibitors, if possible. (7.1)
- Hemorrhage in patients taking warfarin: Monitor changes in prothrombin time or INR. (7.2)

### USE IN SPECIFIC POPULATIONS

- Lactation: Discontinue breast-feeding. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 08/2023

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

### 2 DOSAGE AND ADMINISTRATION

- 2.1 Patient Selection
- 2.2 Recommended Dose
- 2.3 Administration to Patients Who Have Difficulty Swallowing Solids
- 2.4 Dose Modification

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

### 5 WARNINGS AND PRECAUTIONS

- 5.1 Interstitial Lung Disease (ILD)
- 5.2 Hepatotoxicity
- 5.3 Gastrointestinal Perforation
- 5.4 Severe or Persistent Diarrhea
- 5.5 Ocular Disorders including Keratitis
- 5.6 Bullous and Exfoliative Skin Disorders
- 5.7 Embryo-fetal Toxicity

### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

### 7 DRUG INTERACTIONS

- 7.1 Drugs Affecting Gefitinib Exposure
- 7.2 Hemorrhage in Patients taking Warfarin

### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

### 10 OVERDOSAGE

### 11 DESCRIPTION

### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

### 14 CLINICAL STUDIES

### 16 HOW SUPPLIED/STORAGE AND HANDLING

### 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

Gefitinib tablets are indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test [see *Clinical Studies (14)*].

Limitation of Use: Safety and efficacy of gefitinib tablets have not been established in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations [see *Clinical Studies (14)*].

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Patient Selection

Select patients for the first-line treatment of metastatic NSCLC with gefitinib tablets based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in their tumor or plasma specimens [see *Indications and Usage (1)*, *Clinical Studies (14)*]. If these mutations are not detected in a plasma specimen, test tumor tissue if feasible.

Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: <http://www.fda.gov/CompanionDiagnostics>.

#### 2.2 Recommended Dose

The recommended dose of gefitinib tablets is 250 mg orally once daily with or without food until disease progression or unacceptable toxicity.

Do not take a missed dose within 12 hours of the next dose.

#### 2.3 Administration to Patients Who Have Difficulty Swallowing Solids

Immerse gefitinib tablets in 4 to 8 ounces of water by dropping the tablet in water, and stir for approximately 15 minutes. Immediately drink the liquid or administer through a naso-gastric tube. Rinse the container with 4 to 8 ounces of water and immediately drink or administer through the naso-gastric tube.

#### 2.4 Dose Modification

*Dose Modifications for Adverse Drug Reactions*

Withhold gefitinib tablets (for up to 14 days) for any of the following:

- Acute onset or worsening of pulmonary symptoms (dyspnea, cough, fever) [see *Warnings and Precautions (5.1)*]

- NCI CTCAE Grade 2 or higher in ALT and/or AST elevations [*see Warnings and Precautions (5.2)*]
- NCI CTCAE Grade 3 or higher diarrhea [*see Warnings and Precautions (5.4)*]
- Signs and symptoms of severe or worsening ocular disorders including keratitis [*see Warnings and Precautions (5.5)*]
- NCI CTCAE Grade 3 or higher skin reactions [*see Warnings and Precautions (5.6)*]

Resume treatment with gefitinib tablets when the adverse reaction fully resolves or improves to NCI CTCAE Grade 1.

Permanently discontinue gefitinib tablets for:

- Confirmed interstitial lung disease (ILD) [*see Warnings and Precautions (5.1)*]
- Severe hepatic impairment [*see Warnings and Precautions (5.2)*]
- Gastrointestinal perforation [*see Warnings and Precautions (5.3)*]
- Persistent ulcerative keratitis [*see Warnings and Precautions (5.5)*]

#### *Dose Modifications for Drug Interactions*

##### *Strong CYP3A4 Inducers*

Increase gefitinib tablets to 500 mg daily in the absence of severe adverse drug reaction, and resume gefitinib tablets at 250 mg seven days after discontinuation of the strong CYP3A4 inducer [*see Drug Interactions (7), Clinical Pharmacology (12.3)*].

### **3 DOSAGE FORMS AND STRENGTHS**

250 mg tablets: Reddish-brown, round, biconvex coated tablet. Engraved "APO" over "250" on one side, plain on the other side.

### **4 CONTRAINDICATIONS**

None.

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Interstitial Lung Disease (ILD)**

ILD or ILD-like adverse drug reactions (e.g., lung infiltration, pneumonitis, acute respiratory distress syndrome, or pulmonary fibrosis) occurred in 1.3% of the 2462 patients who received gefitinib across clinical trials; of these, 0.7% were Grade 3 or higher and 3 cases were fatal.

Withhold gefitinib tablets and promptly investigate for ILD in any patient who presents with worsening of respiratory symptoms such as dyspnea, cough and fever. Permanently discontinue gefitinib tablets if ILD is confirmed [*see Dosage and Administration (2.4), Adverse Reactions*

(6.1)].

## **5.2 Hepatotoxicity**

In patients who received gefitinib across clinical trials, 11.4% of patients had increased alanine aminotransferase (ALT), 7.9% of patients had increased aspartate aminotransferase (AST), and 2.7% of patients had increased bilirubin. Grade 3 or higher liver test abnormalities occurred in 5.1% (ALT), 3.0% (AST), and 0.7% (bilirubin) of patients. The incidence of fatal hepatotoxicity was 0.04%.

Obtain periodic liver function testing. Withhold gefitinib tablets in patients with worsening liver function and discontinue in patients with severe hepatic impairment [see *Dosage and Administration (2.4)*, *Adverse Reactions (6.1)*, *Use in Specific Populations (8.7)*].

## **5.3 Gastrointestinal Perforation**

Gastrointestinal perforation occurred in three (0.1%) of the 2462 gefitinib-treated patients across clinical trials [see *Adverse Reactions (6.1)*]. Permanently discontinue gefitinib tablets in patients who develop gastrointestinal perforation [see *Dosage and Administration (2.4)*].

## **5.4 Severe or Persistent Diarrhea**

Grade 3 or 4 diarrhea occurred in 3% of 2462 gefitinib-treated patients across clinical trials. Withhold gefitinib tablets for severe or persistent (up to 14 days) diarrhea [see *Dosage and Administration (2.4)*, *Adverse Reactions (6.1)*].

## **5.5 Ocular Disorders including Keratitis**

Ocular disorders [keratitis (0.1%), corneal erosion and aberrant eyelash growth (0.2%), conjunctivitis, blephritis and dry eye (6.7%)] occurred in the 2462 gefitinib-treated patients across clinical trials. The incidence of Grade 3 ocular disorders was 0.1% [see *Adverse Reactions (6.1)*]. Interrupt or discontinue gefitinib tablets for severe, or worsening ocular disorders [see *Dosage and Administration (2.4)*].

## **5.6 Bullous and Exfoliative Skin Disorders**

Bullous conditions including toxic epidermal necrolysis, Stevens Johnson syndrome and erythema multiforme have been reported from treatment with gefitinib. Erythema multiforme and dermatitis bullous have been reported in two patients (0.08%) across NSCLC trials (Study 2, Study 3 and Study 4). Gefitinib tablets treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions.

## **5.7 Embryo-fetal Toxicity**

Based on its mechanism of action and data from animal reproduction studies gefitinib tablets can cause fetal harm when administered to a pregnant woman. In animal reproductive studies, oral administration of gefitinib from organogenesis through weaning resulted in fetotoxicity and

neonatal death at doses below the recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with gefitinib tablets and for at least two weeks following completion of therapy [see *Use in Specific Populations (8.1, 8.3)*].

## 6 ADVERSE REACTIONS

The following adverse drug reactions are discussed in more detail in other sections of the labeling:

- Interstitial Lung Disease [see *Warnings and Precautions (5.1)*]
- Hepatotoxicity [see *Warnings and Precautions (5.2)*]
- Gastrointestinal Perforation [see *Warnings and Precautions (5.3)*]
- Severe or Persistent Diarrhea [see *Warnings and Precautions (5.4)*]
- Ocular Disorders including Keratitis [see *Warnings and Precautions (5.5)*]
- Bullous and Exfoliative Skin Disorders [see *Warning and Precautions (5.6)*]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of gefitinib tablets is based on the data from 2462 patients with NSCLC who received gefitinib 250 mg daily monotherapy in three randomized clinical studies (Study 2, Study 3 and Study 4). Patients with a history of interstitial lung disease, drug-induced interstitial disease, radiation pneumonitis that required steroid treatment or any evidence of clinically active interstitial lung disease were excluded from these studies.

#### Controlled Studies:

Study 2 was a randomized, multicenter, open-label trial in which 1217 patients were randomized to receive first-line treatment for metastatic NSCLC; 607 patients received gefitinib 250 mg daily and 589 patients received carboplatin/paclitaxel. The median duration of treatment with gefitinib was 5.9 months. The study population characteristics were: median age 57 years, age less than 65 years (73%), female (79%), Asian (100%), NSCLC adenocarcinoma histology (100%), never smoker (94%), light ex-smoker (6%), ECOG PS 0 or 1 (90%).

Study 3 was a randomized, multicenter, double-blind, placebo-controlled trial in which 1692 patients were randomized to receive second- or third-line treatment for metastatic NSCLC; of which 1126 patients received gefitinib 250 mg daily and 562 patients received placebo. The median duration of treatment with gefitinib was 2.9 months. The study population characteristics were: median age 62 years, age less than 65 years (60%), female (33%), Caucasian (75%), Asian (21%), NSCLC adenocarcinoma histology (48%), never smoker (22%), ECOG PS 0 or 1 (65%),

PS 2 (29%), PS 3 (5%) and two or more prior therapies (51%).

Study 4 was a randomized, multicenter, open-label trial in which 1466 patients were randomized to receive second-line treatment for metastatic NSCLC; 729 patients received gefitinib 250 mg daily and 715 patients received docetaxel. The median duration of treatment with gefitinib tablets was 2.4 months. The study population characteristics were: median age 61 years, age less than 65 years (61%), female (36%), Caucasian (79%), Asian (21%), NSCLC adenocarcinoma histology (54%), never smoker (20%), ECOG PS 0 or 1 (88%) and two or more prior therapies (16%).

The pooled safety database from the three randomized trials was used to evaluate for serious and uncommon adverse drug reactions. Common adverse reactions were evaluated in Study 3. The most frequent adverse reactions in Study 3 (incidence of >20% and greater than placebo) reported in gefitinib-treated patients were skin reactions (47%) and diarrhea (29%). The most frequent fatal adverse reactions in gefitinib-treated patients were respiratory failure (0.9%), pneumonia (0.8%), and pulmonary embolism (0.5%).

Approximately 5% of gefitinib-treated patients and 2.3% of placebo-treated patients discontinued treatment due to an adverse event. The most frequent adverse reactions that led to discontinuation in patients treated with gefitinib were nausea (0.5%), vomiting (0.5%) and diarrhea (0.4%).

**Table 1- Selected Adverse Drug Reactions Occurring with an Incidence Rate ≥5% and an Increase of >2% of Gefitinib-treated Patients in Study 3**

Adverse Reaction	Percentage (%) of patients			
	Gefitinib (N=1126)		Placebo (N=562)	
	All Grades	Grade 3 and 4	All Grades	Grade 3 and 4
<b>Skin and subcutaneous tissue disorders</b>				
Skin reactions <sup>1</sup>	47%	2%	17%	0.4%
Nail disorders <sup>2</sup>	5%	0.1%	0.7%	0%
<b>Gastrointestinal disorders</b>				
Diarrhea <sup>3</sup>	29%	3%	10%	1%
Vomiting	14%	1.2%	10%	0.4%
Stomatitis <sup>4</sup>	7%	0.3%	4%	0.2%
<b>Metabolism and nutrition disorders</b>				
Decreased appetite	17%	2.3%	14%	2%
<b>Eye disorders</b>				
Conjunctivitis/blepharitis/dry eye <sup>5</sup>	6%	0%	3.2%	0%

<sup>1</sup> Includes Acne, Acne pustular, Dermatitis, Dermatitis acneiform, Dermatitis exfoliative, Drug eruption, Dry skin, Erythema, Exfoliative rash, Folliculitis, Pruritus, Pruritus generalized, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash pustular, Rash vesicular, Skin exfoliation, Skin toxicity, Xeroderma

<sup>2</sup> Includes Ingrowing nail, Nail bed infection, Nail disorder, Nail infection, Onychoclasia, Onycholysis, Paronychia

<sup>3</sup> Includes Diarrhea, Feces soft, Frequent bowel movements

- <sup>4</sup> Includes Aphthous stomatitis, Cheilitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral mucosal blistering, Stomatitis, Tongue disorder, Tongue ulceration
- <sup>5</sup> Includes Blepharitis, Conjunctival hyperemia, Conjunctivitis, Dry eye, Eye irritation, Eye pruritus, Eye swelling, Eyelid irritation, Eyelid edema, Eyelids pruritus

**Table 2 – Treatment Emergent Laboratory Abnormalities Occurring More Frequently in Gefitinib-Treated Patients in Study 3**

Adverse Reaction	Gefitinib		Placebo	
	All Grades %	Grade 3 and 4 %	All Grades %	Grade 3 and 4 %
Alanine aminotransferase increased <sup>1</sup>	38% <sup>2</sup>	2.4%	23% <sup>2</sup>	1.4% <sup>4</sup>
Aspartate aminotransferase increased <sup>1</sup>	40% <sup>3</sup>	2%	25% <sup>3</sup>	1.3% <sup>5</sup>
Proteinuria	35%	4.7%	31%	3.3%

<sup>1</sup> Patients were allowed to enter the clinical study with lab values of ALT or AST CTCAE grade 1 or 2

<sup>2</sup> 14% gefitinib patients and 10% placebo patients were CTC grade 1 or 2 ALT at baseline

<sup>3</sup> 15% gefitinib patients and 12% placebo patients were CTC grade 1 or 2 AST at baseline

<sup>4</sup> 0.2% of placebo patients were CTC grade 3 at baseline

<sup>5</sup> 0.4% of placebo patients were CTC grade 3 at baseline

The following adverse reactions have been reported with gefitinib across NSCLC trials (Study 2, Study 3 and Study 4) and are not listed elsewhere in Section 6: nausea (18%), asthenia (17%), pyrexia (9%), alopecia (4.7%), hemorrhage (including epistaxis and hematuria) (4.3%), dry mouth (2%), dehydration (1.8%) elevations in blood creatinine (1.5%), allergic reactions including angioedema and urticaria (1.1%), palmar-plantar erythrodysesthesia syndrome (0.2%) and pancreatitis (0.1%).

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of gefitinib. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Renal and urinary disorders:* cystitis, hemorrhagic cystitis

*Skin and subcutaneous tissue disorders:* cutaneous vasculitis

## 7 DRUG INTERACTIONS

### 7.1 Drugs Affecting Gefitinib Exposure

#### *CYP3A4 Inducer*

Drugs that are strong inducers of CYP3A4 increase the metabolism of gefitinib and decrease gefitinib plasma concentrations. Increase gefitinib tablets to 500 mg daily in patients receiving a strong CYP3A4 inducer (e.g., rifampicin, phenytoin, or tricyclic antidepressant) and resume gefitinib tablets at 250 mg 7 days after discontinuation of the strong inducer [*see Dosage and Administration (2.4), Clinical Pharmacology (12.3)*].

### *CYP3A4 Inhibitor*

Drugs that are strong inhibitors of CYP3A4 (e.g., ketoconazole and itraconazole) decrease gefitinib metabolism and increase gefitinib plasma concentrations. Monitor adverse reactions when administering strong CYP3A4 inhibitors with gefitinib tablets.

### *Drugs Affecting Gastric pH*

Drugs that elevate gastric pH (e.g., proton pump inhibitors, histamine H<sub>2</sub>-receptor antagonists, and antacids) may reduce plasma concentrations of gefitinib. Avoid concomitant use of gefitinib tablets with proton pump inhibitors, if possible. If treatment with a proton-pump inhibitor is required, take gefitinib tablets 12 hours after the last dose or 12 hours before the next dose of the proton-pump inhibitor. Take gefitinib tablets 6 hours after or 6 hours before an H<sub>2</sub>-receptor antagonist or an antacid [see *Clinical Pharmacology (12.3)*].

## **7.2 Hemorrhage in Patients taking Warfarin**

International Normalized Ratio (INR) elevations and/or hemorrhage have been reported in some patients taking warfarin while on gefitinib therapy. Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

Based on its mechanism of action and animal data, gefitinib tablets can cause fetal harm when administered to a pregnant woman. In animal reproductive studies, oral administration of gefitinib from organogenesis through weaning resulted in fetotoxicity and neonatal death at doses below the recommended human dose (see *Animal Data*). Advise pregnant women of the potential hazard to a fetus or potential risk for loss of the pregnancy.

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the background risk in the U.S. general population of major birth defects is 2 to 4% and miscarriage is 15 to 20% of clinically recognized pregnancies.

#### Data

##### *Animal Data*

A single dose study in rats showed that gefitinib crosses the placenta after an oral dose of 5 mg/kg (30 mg/m<sup>2</sup>, about 0.2 times the recommended human dose on a mg/m<sup>2</sup> basis). When pregnant rats were treated with 5 mg/kg from the beginning of organogenesis to the end of weaning there was a reduction in the number of offspring born alive. This effect was more severe at 20 mg/kg (approximate the human clinical dose on a mg/m<sup>2</sup> basis) and was accompanied by



high neonatal mortality soon after parturition. In rabbits, a dose of 20 mg/kg/day (240 mg/m<sup>2</sup>, about twice the recommended dose in humans on a mg/m<sup>2</sup> basis) caused reduced fetal weight.

## **8.2 Lactation**

### Risk Summary

It is not known whether gefitinib is excreted in human milk. Animal studies indicate the gefitinib and its metabolites are present in rat milk at a concentration higher than those in maternal plasma. Because of the potential for serious adverse reactions in nursing infants from gefitinib, advise women to discontinue breast-feeding during treatment with gefitinib tablets.

### Data

#### *Animal Data*

Levels of gefitinib and its metabolites were 11-to-19-fold higher in milk than in blood, after oral exposure of lactating rats to a dose of 5 mg/kg.

## **8.3 Females and Males of Reproductive Potential**

### Contraception

Based on its mechanism of action and animal data, gefitinib tablets can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with gefitinib tablets and for at least two weeks following completion of therapy.

### Infertility

Gefitinib tablets may result in reduced fertility in females of reproductive potential [*see Nonclinical Toxicology (13.1)*].

## **8.4 Pediatric Use**

The safety and effectiveness of gefitinib in pediatric patients have not been established.

## **8.5 Geriatric Use**

Of the 823 patients enrolled in two randomized, active-controlled clinical trials 374 patients (45%) were 65 years and older, and 93 patients (11%) were 75 years and older. No overall differences in safety were observed between patients 65 years and older and those younger than 65 years. There is insufficient information to assess for differences in efficacy between older and younger patients.

## **8.6 Renal Impairment**

Less than four percent (<4%) of gefitinib and its metabolites are excreted via the kidney. No

clinical studies were conducted with gefitinib in patients with severe renal impairment.

## 8.7 Hepatic Impairment

The systemic exposure of gefitinib was compared in patients with mild, moderate, or severe hepatic impairment due to cirrhosis (according to Child-Pugh classification) and healthy subjects with normal hepatic function (N=10/group). The mean systemic exposure ( $AUC_{0-\infty}$ ) was increased by 40% in patients with mild impairment, 263% in patients with moderate impairment, and 166% in patients with severe hepatic impairment. Monitor adverse reactions when gefitinib tablets are administered to patients with moderate and severe hepatic impairment.

In a study comparing 13 patients with liver metastases and moderate hepatic impairment (addition of CTC grade of baseline AST/SGOT, ALP, and bilirubin equals 3 to 5) to 14 patients with liver metastases and normal hepatic function, the systemic exposure of gefitinib was similar [see *Warnings and Precautions* (5.2)].

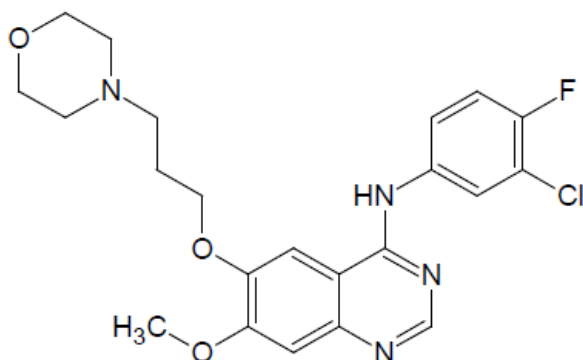
## 10 OVERDOSAGE

Twenty three patients were treated weekly with doses from 1500 mg to 3500 mg, and gefitinib exposure did not increase with increasing dose. Adverse events were mostly mild to moderate in severity, and were consistent with the known safety profile of gefitinib. In the event of suspected overdose, interrupt gefitinib tablets, institute supportive care, and observe until clinical stabilization. There are no specific measures/treatments that should be taken following gefitinib tablets overdosing.

## 11 DESCRIPTION

Gefitinib is a kinase inhibitor.

The chemical name of gefitinib is 4-Quinazolinamine *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl) propoxy] and the following structural formula:



Gefitinib has the molecular formula  $C_{22}H_{24}ClFN_4O_3$ , a relative molecular mass of 446.91 daltons and is a white to off white powder. Gefitinib is a free base. The molecule has  $pK_{as}$  of 5.4 and 7.2. Gefitinib can be defined as sparingly soluble at pH 1, but is practically insoluble above pH 7, with the solubility decreasing sharply between pH 4 and pH 6. In non- aqueous solvents, gefitinib is freely soluble in glacial acetic acid and dimethyl sulfoxide, soluble in pyridine, sparingly soluble in tetrahydrofuran, and slightly soluble in methanol, ethanol (99.5%), ethyl acetate, propan-2-ol and acetonitrile.

Gefitinib tablets are available as reddish-brown, round, biconvex coated tablets containing 250 mg of gefitinib, for oral administration. The inactive ingredients of the tablet core of gefitinib tablets are amino methacrylate copolymer, colloidal silicon dioxide, crospovidone, and magnesium stearate. The tablet coating is composed of ferric oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

The epidermal growth factor receptor (EGFR) is expressed on the cell surface of both normal and cancer cells and plays a role in the processes of cell growth and proliferation. Some EGFR activating mutations (exon 19 deletion or exon 21 point mutation L858R) within NSCLC cells have been identified as contributing to the promotion of tumor cell growth, blocking of apoptosis, increasing the production of angiogenic factors and facilitating the processes of metastasis.

Gefitinib reversibly inhibits the kinase activity of wild-type and certain activating mutations of EGFR, preventing autophosphorylation of tyrosine residues associated with the receptor, thereby inhibiting further downstream signaling and blocking EGFR-dependent proliferation.

Gefitinib binding affinity for EGFR exon 19 deletion or exon 21 point mutation L858R mutations is higher than its affinity for the wild-type EGFR. Gefitinib also inhibits IGF and PDGF-mediated signaling at clinically relevant concentrations; inhibition of other tyrosine kinase receptors has not been fully characterized.

### **12.3 Pharmacokinetics**

#### *Absorption and Distribution*

The mean oral bioavailability of gefitinib is 60%, with peak plasma levels occurring 3 to 7 hours after dosing. Food does not alter gefitinib bioavailability to a clinically meaningful extent. Gefitinib tablets can be administered with or without 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  $\alpha$ 1-acid glycoprotein) is 90%, independent of drug concentrations. Gefitinib is a substrate for the membrane transport P- glycoprotein (P-gp), but it is unlikely to influence gefitinib absorption

as P-gp is saturated at higher 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 have been fully identified in fecal extracts and the major active component was O-desmethyl gefitinib produced by CYP2D6 metabolism and accounted for 14% of the dose.

Eight 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 of 48 hours after intravenous administration. The inter-subject variability (coefficient of variation) for AUC in healthy subjects was 67%. Daily oral administration of gefitinib to cancer patients resulted in a two-fold accumulation compared to single dose administration. Steady state plasma concentrations are achieved within 10 days after daily dosing. Excretion of gefitinib and its metabolites is predominantly via the feces (86%), with renal elimination accounting for less than 4% of the administered dose.

### *Specific Populations*

*Age, gender, body weight, ethnicity or renal function:* Population pharmacokinetic analyses suggest that patient age, body weight, ethnicity (populations included) or creatinine clearance (above 20 mL/min) has no clinically meaningful effect on predicted steady state trough concentration of gefitinib. Population pharmacokinetic analyses of Study 1 showed that women had 27% higher exposure than men; however, this difference was not identified in the analyses of other gefitinib clinical studies. No dose adjustment based on patient gender is recommended.

*Hepatic Impairment:* The systemic exposure of gefitinib was compared between patients with mild, moderate, or severe hepatic impairment due to cirrhosis (according to Child-Pugh classification) and healthy subjects with normal hepatic function (N=10/group). The mean systemic exposure (AUC<sub>0-∞</sub>) was increased by 40% in patients with mild impairment, 263% in patients with moderate impairment, and 166% in patients with severe hepatic impairment. In a study comparing 13 patients with liver metastases and moderate hepatic impairment to 14 patients with liver metastases and normal hepatic function, the systemic exposure of gefitinib was similar [see [Warnings and Precautions \(5.2\)](#), [Use in Specific Populations \(8.7\)](#)].

*CYP2D6 Poor metabolizer:* CYP2D6 metabolizes gefitinib to O-desmethyl gefitinib *in vitro*.

In healthy CYP2D6 poor metabolizers, O-desmethyl gefitinib concentration was not measurable and the mean exposure to gefitinib was 2-fold higher as compared to the extensive metabolizers. This increase in exposure in CYP2D6 poor metabolizers may be clinically important because some adverse drug reactions are related to higher exposure of gefitinib. No dose adjustment is recommended in patients with a known CYP2D6 poor metabolizer genotype, but these patients should be closely monitored for adverse reactions. The impact of CYP2D6 inhibiting drugs on gefitinib pharmacokinetics has not been evaluated. However, similar precautions should be used when administering CYP2D6 inhibitors with gefitinib because of the possibility of increased exposure in these patients.

An exploratory exposure response analysis showed an increase in the incidence of interstitial lung disease (ILD) with a greater than 2-fold increase in the gefitinib exposure [see [Warnings and Precautions \(5.1\)](#)].

#### *Drug-Drug Interactions*

##### *Strong CYP3A4 Inducer:*

Concomitant administration of rifampicin (600 mg QD for 16 days), a strong inducer of CYP3A4, with gefitinib (500 mg single dose on Day 10 of gefitinib administration) reduced mean AUC of gefitinib by 83% [see [Dosage and Administration \(2.4\)](#), [Drug Interactions \(7\)](#)].

##### *CYP3A4 Inhibitor:*

Concomitant administration of itraconazole (200 mg QD for 12 days), an inhibitor of CYP3A4, with gefitinib (250 mg single dose on Day 4 of itraconazole administration) to healthy male subjects, increased mean gefitinib AUC by 80% [see [Drug Interactions \(7\)](#)].

##### *Drugs Affecting Gastric pH:*

Co-administration of high doses of ranitidine with sodium bicarbonate (to maintain the gastric pH above pH 5.0) to healthy subjects decreased mean gefitinib AUC by 47% [see [Drug Interactions \(7\)](#)].

In human liver microsome studies, gefitinib had no inhibitory effect on CYP1A2, CYP2C9, and CYP3A4 activities at concentrations ranging from 2 to 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 on Day 15 of gefitinib dosing (500 mg daily for 28 days) in patients with solid tumors.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Gefitinib has been tested for genotoxicity in a series of *in vitro* (bacterial mutation, mouse lymphoma, and human lymphocyte) assays and an *in vivo* rat micronucleus test. Under the conditions of these assays, gefitinib did not cause genetic damage.

In a two-year carcinogenicity study in mice, administration of gefitinib at a dose of 270 mg/m<sup>2</sup>/day (approximately twice the recommended daily dose of 250 mg on a mg/m<sup>2</sup> basis; dose reduced from 375 mg/m<sup>2</sup>/day from week 22) caused hepatocellular adenomas in females. In a two-year carcinogenicity study in rats, administration of gefitinib at 60 mg/m<sup>2</sup>/day (approximately 0.4 times the recommended daily clinical dose on a mg/m<sup>2</sup> basis) caused hepatocellular adenomas and hemangiomas/hemangiosarcomas of the mesenteric lymph nodes in female rats. The clinical relevance of these findings is unknown.

In a dedicated fertility study in rats at doses  $\geq 120$  mg/m<sup>2</sup> (approximately equal to the recommended human dose of gefitinib on a mg/m<sup>2</sup> basis), animals presented with an increased incidence of irregular estrous, decreased corpora lutea, and decreases in uterine implants and live embryos per litter.

## 14 CLINICAL STUDIES

### Non-Small Cell Lung Cancer (NSCLC)

#### *Study 1*

The efficacy and safety of gefitinib for the first-line treatment of patients with metastatic NSCLC containing EGFR exon 19 deletions or L858R substitution mutations was demonstrated in a multicenter, single-arm, open-label clinical study (Study 1). A total of 106 treatment-naïve patients with metastatic EGFR mutation positive NSCLC received gefitinib at a dose of 250 mg once daily until disease progression or intolerable toxicity. The major efficacy outcome measure was objective response rate (ORR) according to RECIST v1.1 as evaluated by both a Blinded Independent Central Review (BICR) and investigators. Duration of response (DOR) was an additional outcome measure. Eligible patients were required to have a deletion in EGFR exon 19 or L858R, L861Q, or G719X substitution mutation and no T790M or S768I mutation or exon 20 insertion in tumor specimens as prospectively determined by a clinical trial assay. Tumor samples from 87 patients were tested retrospectively using the *therascreen*<sup>®</sup> EGFR RGQ PCR Kit.

The study population characteristics were: median age 65 years, age 75 years or older (25%), age less than 65 years (49%), white (100%), female (71%), never smokers (64%), WHO PS 0 (45%), WHO PS 1 (48%), WHO PS 2 (7%), and adenocarcinoma histology (97%). Sixty patients had exon 19 deletions (65%), 29 patients had L858R substitution (31%), while two patients each had tumors harboring L861Q or G719X substitution mutation.

The median duration of treatment was 8.0 months. Efficacy results from Study 1 are summarized below.

**Table 3 – Efficacy Results in Study 1**

Efficacy Parameter	BICR <sup>1</sup> Assessment (n=106) <sup>2</sup>	Investigator Assessment (n=106)
Objective Response Rate <sup>3</sup> (95% CI)	50% (41, 59)	70% (61, 78)
Complete Response Rate	0.9%	1.9%
Partial Response Rate	49%	68%
Median Duration of Response (months) (95% CI)	6 (5.6, 11.1)	8.3 (7.6, 11.3)

<sup>1</sup> BICR, Blinded Independent Central Review

<sup>2</sup> 17 patients without target lesion at baseline detected by BICR were deemed non responders

<sup>3</sup> Determined by RECIST v 1.1

The response rates were similar in patients whose tumors had EGFR exon 19 deletions and exon 21 L858R substitution mutations. Two partial responses were observed in both patients whose tumors had G719X substitution mutation with duration of response of at least 2.8 months and 5.6 months, respectively. One of two patients whose tumors had L861Q substitution mutation also achieved a partial response with duration of response of at least 2.8 months.

### *Study 2*

The results of Study 1 were supported by an exploratory analysis of a subset of a randomized, multicenter, open-label trial (Study 2) conducted in patients with metastatic adenocarcinoma histology NSCLC receiving first-line treatment. Patients were randomized (1:1) to receive gefitinib 250 mg orally once daily or up to 6 cycles of carboplatin/paclitaxel. The efficacy outcomes included progression-free survival (PFS) and objective response rate (ORR) as assessed by BICR.

The subset population consisted of 186 of 1217 patients (15%) determined to be EGFR positive by the same clinical trial assay as used in Study 1 and had radiographic scans available for a retrospective assessment by BICR. In this subset, there were 88 gefitinib-treated patients and 98 carboplatin/paclitaxel-treated patients.

Demographic and baseline characteristics of this subset were a median age of 59 years, age 75 years or older (7%), age less than 65 (70%), Asian (100%), female (83%), never smokers (96%), adenocarcinoma histology (100%), and PS 0 to 1 (94%).

The median duration of treatment for gefitinib-treated patients was 9.8 months. The hazard ratio for PFS favored the gefitinib-treated patients [HR of 0.54 (95% CI: 0.38, 0.79)] with a

median PFS of 10.9 months for the gefitinib-treated patients and 7.4 months for the carboplatin/paclitaxel-treated patients as assessed by BICR. In addition, the objective response rate was 67% (95% CI: 56, 77) for gefitinib-treated patients and 41% (95% CI: 31, 51) for carboplatin/paclitaxel-treated patients based on BICR assessment. The median duration of response was 9.6 months for gefitinib-treated patients and 5.5 months for carboplatin/paclitaxel-treated patients.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Gefitinib tablets are available as 250 mg tablets.

Gefitinib tablets 250 mg are reddish-brown, round, biconvex coated tablets. Engraved "APO" over "250" on one side, plain on the other side.

Gefitinib tablets are supplied as:

Bottle of 30 tablets NDC 60505-4512-3

Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labelling ([Patient Information](#)).

Interstitial Lung Disease: Advise patients to immediately contact their healthcare provider for new onset or worsening of pulmonary symptoms such as dyspnea, cough and fever [see [Warnings and Precautions \(5.1\)](#)].

Hepatotoxicity: Inform patients that they will need to undergo lab tests to monitor for liver function. Advise patients to contact their healthcare provider to report any new symptoms indicating hepatic toxicity [see [Warnings and Precautions \(5.2\)](#)].

Gastrointestinal Perforation: Advise patients that gefitinib tablets can increase the risk of gastrointestinal perforation and to seek immediate medical attention for severe abdominal pain [see [Warnings and Precautions \(5.3\)](#)].

Severe or Persistent Diarrhea: Advise patients to contact their healthcare provider for severe or persistent diarrhea [see [Warnings and Precautions \(5.4\)](#)].

Ocular Disorders including Keratitis: Advise patients promptly to contact their healthcare provider if they develop eye symptoms, lacrimation, light sensitivity, blurred vision, eye pain, red eye or changes in vision [see [Warnings and Precautions \(5.5\)](#)]

Bullous and Exfoliative Skin Disorders: Advise patients that gefitinib tablets can increase the risk of bullous and exfoliative skin disorders and to seek immediately medical attention for



severe skin reactions [*see Warnings and Precautions (5.6)*].

Embryo-fetal Toxicity: Advise pregnant women of the potential risk to a fetus or potential risk for loss of the pregnancy [*see Warnings and Precautions (5.7), Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with gefitinib tablets and for at least two weeks following completion of therapy [*see Use in Specific Populations (8.3)*].

Lactation: Advise women to discontinue breast-feeding during treatment with gefitinib tablets [*see Use in Specific Populations (8.2)*].

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**APOTEX INC.  
GEFITINIB TABLETS  
250 mg**

**Manufactured by:**

Apotex Inc.  
Toronto, Ontario  
Canada M9L 1T9

**Manufactured for:**

Apotex Corp.  
Weston, Florida  
USA 33326

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