GILOTRIF- afatinib tablet, film coated
Boehringer Ingelheim Pharmaceuticals, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GILOTRIF safely and effectively. See full prescribing information for GILOTRIF.
GILOTRIF® (afatinib) tablets, for oral use
Initial U.S. Approval: 2013

RECENT MAJOR CHANGES

Indications and Usage,	
Previously Treated, Metastatic Squamous NSCLC (1.2)	4/2016
Dosage and Administration, Recommended Dose (2.2)	4/2016
Warnings and Precautions (5)	4/2016

INDICATIONS AND USAGE

GILOTRIF is a kinase inhibitor indicated for:

- 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 (1.1)
  Limitation of Use: Safety and efficacy of GILOTRIF were not established in patients whose tumors have other EGFR mutations (1.1)
- Treatment of patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy (1.2)

DOSAGE AND ADMINISTRATION

- Recommended dose: 40 mg orally, once daily (2.2)
- Renal impairment: 30 mg orally, once daily in patients with severe renal impairment (2.2, 8.6, 12.3)
- Instruct patients to take GILOTRIF at least 1 hour before or 2 hours after a meal (2)

DOSAGE FORMS AND STRENGTHS

Tablets: 40 mg, 30 mg, and 20 mg (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Diarrhea: Diarrhea may result in dehydration and renal failure. Withhold GILOTRIF for severe and prolonged diarrhea not responsive to anti-diarrheal agents. (2.3, 5.1)
- Bullous and exfoliative skin disorders: Severe bullous, blistering, and exfoliating lesions occurred in 0.2% of patients. Discontinue for life-threatening cutaneous reactions. Withhold GILOTRIF for severe and prolonged cutaneous reactions. (2.3, 5.2)
- Interstitial lung disease (ILD): Occurs in 1.6% of patients. Withhold GILOTRIF for acute onset or worsening of pulmonary symptoms. Discontinue GILOTRIF if ILD is diagnosed. (2.3, 5.3)
- Hepatic toxicity: Fatal hepatic impairment occurs in 0.2% of patients. Monitor with periodic liver testing. Withhold or discontinue GILOTRIF for severe or worsening liver tests. (2.3, 5.4)
- Keratitis: Occurs in 0.7% of patients. Withhold GILOTRIF for keratitis evaluation. Withhold or discontinue GILOTRIF for confirmed ulcerative keratitis. (2.3, 5.5)
- Embryo-fetal toxicity: Can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to the fetus and to use effective contraception. (5.6)

ADVERSE REACTIONS

Most common adverse reactions (≥20%) were diarrhea, rash/acneiform dermatitis, stomatitis, paronychia, dry skin, decreased appetite, nausea, vomiting, pruritus (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Co-administration of P-gp inhibitors can increase afatinib exposure. Reduce GILOTRIF by 10 mg per day if not tolerated. Co-administration of chronic P-gp inducers orally can decrease afatinib exposure. Increase GILOTRIF by 10 mg per day as tolerated. (2.3, 7)

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed (8.2)

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

Revised: 4/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 EGFR Mutation-Positive, Metastatic Non-Small Cell Lung Cancer
1.2 Previously Treated, Metastatic Squamous NSCLC
2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection for EGFR Mutation-Positive Metastatic NSCLC
2.2 Recommended Dose
2.3 Dose Modifications for Adverse Reactions
2.4 Dose Modifications for Drug Interactions
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Diarrhea
5.2 Bullous and Exfoliative Skin Disorders
5.3 Interstitial Lung Disease (ILD)
5.4 Hepatic Toxicity
5.5 Keratitis
5.6 Embryo-Fetal Toxicity
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
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
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES

14.1 EGFR Mutation-Positive Non-Small Cell Lung Cancer
14.2 Previously Treated, Metastatic Squamous NSCLC
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

1.1 EGFR Mutation-Positive, Metastatic Non-Small Cell Lung Cancer

GILOTRIF is 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 (14.1)]*.

Limitation of Use: The safety and efficacy of GILOTRIF have not been established in patients whose tumors have other EGFR mutations *[see Clinical Studies (14.1)]*.

1.2 Previously Treated, Metastatic Squamous NSCLC

GILOTRIF is indicated for the treatment of patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for EGFR Mutation-Positive Metastatic NSCLC

Select patients for first-line treatment of metastatic NSCLC with GILOTRIF based on the presence of EGFR exon 19 deletions or exon 21 (L858R) substitution mutations in tumor specimens *[see Indications and Usage (1.1) and Clinical Studies (14.1)]*. 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 GILOTRIF is 40 mg orally, once daily until disease progression or no longer tolerated by the patient.

Severe Renal Impairment
The recommended dose of GILOTRIF in patients with severe renal impairment (estimated glomerular filtration rate [eGFR*] 15 to 29 mL/min /1.73 m^2) is 30 mg orally, once daily *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

*Use the Modification of Diet in Renal Disease [MDRD] formula to estimate eGFR.

Take GILOTRIF at least 1 hour before or 2 hours after a meal.

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

2.3 Dose Modifications for Adverse Reactions

Withhold GILOTRIF for any adverse reactions of:
- NCI CTCAE* Grade 3 or higher
- Diarrhea of Grade 2 or higher persisting for 2 or more consecutive days while taking anti-diarrheal medication *[see Warnings and Precautions (5.1)]*
- Cutaneous reactions of Grade 2 that are prolonged (lasting more than 7 days) or intolerable *[see Warnings and Precautions (5.2)]*
- Renal impairment of Grade 2 or higher *[see Warnings and Precautions (5.1)]*

*National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), v 3.0

Resume treatment when the adverse reaction fully resolves, returns to baseline, or improves to Grade 1. Reinstitute GILOTRIF at a reduced dose, i.e., 10 mg per day less than the dose at which the adverse reaction occurred.

Permanently discontinue GILOTRIF for:
- Life-threatening bullous, blistering, or exfoliative skin lesions *[see Warnings and Precautions (5.2)]*
- Confirmed interstitial lung disease (ILD) *[see Warnings and Precautions (5.3)]*
- Severe drug-induced hepatic impairment *[see Warnings and Precautions (5.4)]*
- Persistent ulcerative keratitis *[see Warnings and Precautions (5.5)]*
- Symptomatic left ventricular dysfunction *[see Adverse Reactions (6.1)]*
- Severe or intolerable adverse reaction occurring at a dose of 20 mg per day

2.4 Dose Modifications for Drug Interactions

P-gp Inhibitors
Reduce GILOTRIF daily dose by 10 mg if not tolerated for patients who require therapy with a P-glycoprotein (P-gp) inhibitor. Resume the previous dose after discontinuation of the P-gp inhibitor as tolerated *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

P-gp Inducers
Increase GILOTRIF daily dose by 10 mg as tolerated for patients who require chronic therapy with a P-gp inducer. Resume the previous dose 2 to 3 days after discontinuation of the P-gp inducer *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

GILOTRIF is available as:
40 mg tablets: light blue, film-coated, round, biconvex, bevel-edged tablets debossed with “T40” on one side and the Boehringer Ingelheim company symbol on the other side.

30 mg tablets: dark blue, film-coated, round, biconvex, bevel-edged tablets debossed with “T30” on one side and the Boehringer Ingelheim company symbol on the other side.

20 mg tablets: white to slightly yellowish, film-coated, round, biconvex, bevel-edged tablets debossed with “T20” on one side and the Boehringer Ingelheim company symbol on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea

Diarrhea has resulted in dehydration with or without renal impairment across the clinical experience; some cases were fatal. Grade 3-4 diarrhea occurred in 697 (16%) of the 4257 patients who received GILOTRIF across 44 clinical trials. In Study 1, diarrhea occurred in 96% of patients treated with GILOTRIF (n=229), of which 15% were Grade 3 in severity and occurred within the first 6 weeks. Renal impairment as a consequence of diarrhea occurred in 6% of patients treated with GILOTRIF, of which 1.3% were Grade 3. In Study 2, diarrhea occurred in 75% of patients treated with GILOTRIF

(n=392), of which 10% were Grade 3 in severity and 0.8% were Grade 4 in severity. Renal impairment as a consequence of diarrhea occurred in 7% of patients treated with GILOTRIF, of which 2% were Grade 3 *[see Adverse Reactions (6.1)]*.

For patients who develop prolonged Grade 2 diarrhea lasting more than 48 hours, or greater than or equal to Grade 3 diarrhea, withhold GILOTRIF until diarrhea resolves to Grade 1 or less, and resume GILOTRIF with appropriate dose reduction *[see Dosage and Administration (2.3)]*. Provide patients with an anti-diarrheal agent (e.g., loperamide) for self-administration at the onset of diarrhea and instruct patients to continue anti-diarrheal therapy until loose bowel movements cease for 12 hours.

5.2 Bullous and Exfoliative Skin Disorders

Grade 3 cutaneous reactions characterized by bullous, blistering, and exfoliating lesions, occurred in 0.2% of the 4257 patients who received GILOTRIF across clinical trials. In Study 1, the overall incidence of cutaneous reactions consisting of rash, erythema, and acneiform rash was 90%, and the incidence of Grade 3 cutaneous reactions was 16%. In addition, the incidence of Grade 1-3 palmar-plantar erythrodysesthesia syndrome was 7%. In Study 2, the overall incidence of cutaneous reactions consisting of rash, erythema, and acneiform rash was 70%, and the incidence of Grade 3 cutaneous reactions was 7%. In addition, the incidence of Grade 1-3 palmar-plantar erythrodysesthesia syndrome was 1.5% *[see Adverse Reactions (6.1)]*.

Discontinue GILOTRIF in patients who develop life-threatening bullous, blistering, or exfoliating lesions. For patients who develop prolonged Grade 2 cutaneous adverse reactions lasting more than 7 days, intolerable Grade 2, or Grade 3 cutaneous reactions, withhold GILOTRIF until the adverse reaction resolves to Grade 1 or less, and resume GILOTRIF with appropriate dose reduction *[see Dosage and Administration (2.3)]*.

Postmarketing cases consistent with toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (SJS) have been reported in patients receiving GILOTRIF. The cases of TEN and SJS bullous skin reactions result from a distinct and separate mechanism of toxicity than the bullous skin lesions secondary to the pharmacologic action of the drug on the epidermal growth factor receptor. Discontinue GILOTRIF if TEN or SJS is suspected *[see Dosage and Administration (2.3)]*.

5.3 Interstitial Lung Disease (ILD)

Interstitial lung disease or ILD-like adverse reactions (e.g., lung infiltration, pneumonitis, acute respiratory distress syndrome, or alveolitis allergic) occurred in 1.6% of the 4257 patients who received GILOTRIF across clinical trials; of these, 0.4% were fatal. The incidence of ILD appeared to be higher in Asian patients (2.3%; 38/1657) as compared to Whites (1.0%; 23/2241). In Study 1, the incidence of Grade ≥3 ILD was 1.3% and resulted in death in 1% of GILOTRIF-treated patients. In Study 2, the incidence of Grade ≥3 ILD was 0.9% and resulted in death in 0.8% of GILOTRIF-treated patients.

Withhold GILOTRIF during evaluation of patients with suspected ILD, and discontinue GILOTRIF in patients with confirmed ILD *[see Dosage and Administration (2.3)]*.

5.4 Hepatic Toxicity

In 4257 patients who received GILOTRIF across clinical trials, 9.7% had liver test abnormalities, of which 0.2% were fatal. In Study 1, liver test abnormalities of any grade occurred in 17.5% of the patients treated with GILOTRIF, of which 3.5% had Grade 3-4 liver test abnormalities. In Study 2, liver test abnormalities of any grade occurred in 6% of the patients treated with GILOTRIF, of which 0.2% had Grade 3-4 liver test abnormalities.

Obtain periodic liver testing in patients during treatment with GILOTRIF. Withhold GILOTRIF in patients who develop worsening of liver function *[see Dosage and Administration (2.3)]*. In patients who develop severe hepatic impairment while taking GILOTRIF, treatment should be discontinued.

5.5 Keratitis

Keratitis, characterized as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain, and/or red eye occurred in 0.7% of patients treated with GILOTRIF among 4257 patients across clinical trials, of which 0.05% of patients experienced Grade 3 keratitis. Keratitis was reported in 2.2% patients in Study 1, with Grade 3 in 0.4%. In Study 2, keratitis was reported in 0.3% patients; there were no patients with ≥Grade 3 keratitis.

Withhold GILOTRIF during evaluation of patients with suspected keratitis, and if diagnosis of ulcerative keratitis is confirmed, treatment with GILOTRIF should be interrupted or discontinued *[see Dosage and Administration (2.3)]*. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. GILOTRIF should be used with caution in patients with a history of keratitis, ulcerative keratitis, or severe dry eye *[see Adverse Reactions (6.1)]*. Contact lens use is also a risk factor for keratitis and ulceration.

5.6 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, GILOTRIF can cause fetal harm when administered to a pregnant woman. Administration of afatinib to pregnant rabbits during organogenesis at exposures approximately 0.2 times the exposure in humans at the recommended dose of 40 mg daily resulted in embryotoxicity and, in rabbits showing maternal toxicity, increased abortions at late gestational stages. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment, and for at least 2 weeks after the last dose of GILOTRIF *[see Use in Specific Populations (8.1 and 8.3)]*.

6 ADVERSE REACTIONS

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

- Diarrhea *[see Warnings and Precautions (5.1)]*
- Bullous and Exfoliative Skin Disorders *[see Warnings and Precautions (5.2)]*
- Interstitial Lung Disease *[see Warnings and Precautions (5.3)]*
- Hepatic Toxicity *[see Warnings and Precautions (5.4)]*
- Keratitis *[see Warnings and Precautions (5.5)]*

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 data in the Warnings and Precautions section reflect exposure to GILOTRIF for clinically significant adverse reactions in 4257 patients enrolled in Studies 1 (n=229) and 2 (n=392), and 3636 patients with cancer enrolled in 42 studies of GILOTRIF administered alone or in combination with other anti-neoplastic drugs at GILOTRIF doses ranging from 10-70 mg daily or at doses 10-160 mg in other regimens. The mean exposure was 5.5 months. The population included patients with various cancers, the most common of which were NSCLC, breast, colorectal, brain, and head and neck.

The data described below reflect exposure to GILOTRIF as a single agent in Study 1, a randomized, active-controlled trial conducted in patients with EGFR mutation-positive, metastatic NSCLC, and in Study 2, a randomized, active-controlled trial in patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy.

<u>EGFR Mutation-Positive, Metastatic NSCLC</u>

The data in Tables 1 and 2 below reflect the exposure of 229 EGFR-tyrosine kinase inhibitor-naïve, GILOTRIF-treated patients with EGFR mutation-positive, metastatic, non-squamous NSCLC enrolled in

a randomized, multicenter, open-label trial (Study 1). Patients received GILOTRIF 40 mg daily until documented disease progression or intolerance to the therapy. A total of 111 patients were treated with pemetrexed/cisplatin. Patients were treated with pemetrexed 500 mg/m^2 followed after 30 minutes by cisplatin 75 mg/m^2 every three weeks for a maximum of six treatment courses.

The median exposure was 11 months for patients treated with GILOTRIF and 3.4 months for patients treated with pemetrexed/cisplatin. The overall trial population had a median age of 61 years; 61% of patients in the GILOTRIF arm and 60% of patients in the pemetrexed/cisplatin arm were younger than 65 years. A total of 64% of patients on GILOTRIF and 67% of pemetrexed/cisplatin patients were female. More than two-thirds of patients were from Asia (GILOTRIF 70%; pemetrexed/cisplatin 72%).

Serious adverse reactions were reported in 29% of patients treated with GILOTRIF. The most frequent serious adverse reactions reported in patients treated with GILOTRIF were diarrhea (6.6%); vomiting (4.8%); and dyspnea, fatigue, and hypokalemia (1.7% each). Fatal adverse reactions in GILOTRIF-treated patients in Study 1 included pulmonary toxicity/ILD-like adverse reactions (1.3%), sepsis (0.43%), and pneumonia (0.43%).

Dose reductions due to adverse reactions were required in 57% of GILOTRIF-treated patients. The most frequent adverse reactions that led to dose reduction in the patients treated with GILOTRIF were diarrhea (20%), rash/acne (19%), paronychia (14%), and stomatitis (10%).

Discontinuation of therapy in GILOTRIF-treated patients for adverse reactions was 14.0%. The most frequent adverse reactions that led to discontinuation in GILOTRIF-treated patients were diarrhea (1.3%), ILD (0.9%), and paronychia (0.9%).

Clinical trials of GILOTRIF excluded patients with an abnormal left ventricular ejection fraction (LVEF), i.e., below the institutional lower limit of normal. In Study 1, all patients were evaluated for LVEF at screening and every 9 weeks thereafter in the GILOTRIF-treated group and as needed in the pemetrexed/cisplatin group. More GILOTRIF-treated patients (2.2%; n=5) experienced ventricular dysfunction (defined as diastolic dysfunction, left ventricular dysfunction, or ventricular dilation; all < Grade 3) compared to chemotherapy-treated patients (0.9%; n=1).

Tables 1 and 2 summarize common adverse reactions and laboratory abnormalities in Study 1.

Table 1 Adverse Reactions Reported in ≥10% of GILOTRIF-Treated Patients in Study 1*

Adverse Reaction	GILOTRIF n=229		Pemetrexed/Cisplatin n=111	
	All Grades (%)	Grade 3† (%)	All Grades (%)	Grade 3† (%)
Gastrointestinal disorders				
Diarrhea	96	15	23	2
Stomatitis[1]	71	9	15	1
Cheilitis	12	0	1	0
Skin and subcutaneous tissue disorders				
Rash/acneiform dermatitis[2]	90	16	11	0
Pruritus	21	0	1	0
Dry skin	31	0	2	0
Infections				
Paronychia[3]	58	11	0	0
Cystitis	13	1	5	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	17	0	2	1
Rhinorrhea	11	0	6	0
Investigations				
Weight decreased	17	1	14	1
General disorders and administration site conditions				
Pyrexia	12	0	6	0
Eye disorders				
Conjunctivitis	11	0	3	0

*NCI CTCAE v 3.0
†None of the adverse reactions in this table except stomatitis (one patient on GILOTRIF [0.4%]) were Grade 4 in severity.
[1]Includes stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration
[2]Includes acne, acne pustular, dermatitis, acneiform dermatitis, dermatosis, drug eruption, erythema, exfoliative rash, folliculitis, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin disorder, skin erosion, skin exfoliation, skin fissures, skin lesion, skin reaction, skin toxicity, skin ulcer
[3]Includes paronychia, nail infection, nail bed infection

Other clinically important adverse reactions observed in patients treated with GILOTRIF but that occurred at a higher incidence in pemetrexed/cisplatin-treated patients and not listed elsewhere in section 6 include: decreased appetite (29% Grade 1-4, 4% Grade 3), nausea (25% Grade 1-4, 4% Grade 3), and vomiting (23% Grade 1-4, 4% Grade 3).

Table 2 Laboratory Abnormalities Occurring in ≥10% of GILOTRIF Arm and at ≥2% Higher Incidence than in Chemotherapy Arm in Study 1*

Laboratory Abnormality	GILOTRIF n=229		Pemetrexed/Cisplatin n=111	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased alanine aminotransferase (ALT)	54	2	27	1
Increased alkaline phosphate	51	3	46	1
Decreased creatinine clearance	49	2	47	1
Increased aspartate aminotransferase (AST)	46	3	22	1
Decreased lymphocytes	38	9	32	14
Decreased potassium	30	8	11	3
Increased bilirubin	16	1	8	0

*NCI CTCAE v 3.0

Previously Treated, Metastatic Squamous NSCLC

The safety of GILOTRIF was evaluated in 392 GILOTRIF-treated patients with metastatic squamous NSCLC enrolled in a randomized, multicenter, open-label trial (Study 2). Patients were required to have received at least four cycles of platinum-based chemotherapy, ECOG Performance Status (PS) 0 or 1, and normal left ventricular ejection fraction (LVEF). Patients received GILOTRIF 40 mg once daily (n=392) or erlotinib 150 mg once daily (n=395). Treatment continued until documented disease progression or intolerance to the therapy.

Among the 392 GILOTRIF-treated patients, the median age was 65 years, 53% were 65 years of age or older, 84% were male, 72% were White, 25% were Asian, ECOG PS 0 (32%) or 1 (68%). The median exposure was 2.1 months for patients treated with GILOTRIF, 15% were exposed for at least 6 months, and 5% were exposed for at least 12 months.

Serious adverse reactions occurred in 44% of patients treated with GILOTRIF. The most frequent serious adverse reactions in patients treated with GILOTRIF were pneumonia (6.6%), diarrhea (4.6%),

and dehydration and dyspnea (3.1% each). Fatal adverse reactions in GILOTRIF-treated patients included ILD (0.5%), pneumonia (0.3%), respiratory failure (0.3%), acute renal failure (0.3%), and general physical health deterioration (0.3%).

Dose reductions due to adverse reactions were required in 27% of GILOTRIF-treated patients and discontinuation of GILOTRIF for adverse reactions was required for 20%. The most frequent adverse reactions that led to dose reduction in the patients treated with GILOTRIF were diarrhea (15%), rash/acne (5.9%), and stomatitis (3.1%). The most frequent adverse reactions that led to discontinuation in GILOTRIF-treated patients were diarrhea (4.1%) and rash/acne (2.6%). Tables 3 and 4 summarize common adverse reactions and laboratory abnormalities in Study 2.

Table 3 Adverse Reactions Reported in ≥10% of GILOTRIF-Treated Patients in Study 2*

Adverse Reaction	GILOTRIF n=392		Erlotinib n=395	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Gastrointestinal disorders				
Diarrhea	75	11	41	3
Stomatitis[1]	30	4	11	1
Nausea	21	2	16	1
Vomiting	13	1	10	1
Skin and subcutaneous tissue disorders				
Rash/acneiform dermatitis[2]	70	7	70	11
Pruritus	10	0	13	0
Infections				
Paronychia[3]	11	1	5	0
Metabolism and nutrition disorders				
Decreased appetite	25	3	26	2

*NCI CTCAE v 3.0
[1]Includes stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration
[2]Includes acne, dermatitis, acneiform dermatitis, eczema, erythema, exfoliative rash, folliculitis, rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin exfoliation, skin fissures, skin lesion, skin reaction, skin toxicity, skin ulcer
[3]Includes paronychia, nail infection, nail bed infection

Table 4 Laboratory Abnormalities Occurring in ≥10% of GILOTRIF Arm and at ≥2% Higher Incidence than in Erlotinib Arm in Study 2*

Laboratory Abnormality	GILOTRIF n=392		Erlotinib n=395	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased alkaline phosphate	34	2	31	0
Decreased white blood cell count	12	1	8	1
Decreased potassium	11	1	8	1

*NCI CTCAE v 3.0

Other clinically important laboratory abnormalities observed in patients treated with GILOTRIF that are not listed in Table 4 are: increased alanine aminotransferase (10% Grade 1-4; 1% Grade 3-4), increased aspartate aminotransferase (7% Grade 1-4; 1% Grade 3-4), and increased bilirubin (3% Grade 1-4; 0 Grade 3-4).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of GILOTRIF. 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.

- Pancreatitis

7 DRUG INTERACTIONS

Effect of P-glycoprotein (P-gp) Inhibitors and Inducers
Concomitant taking of P-gp inhibitors (including but not limited to ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) with GILOTRIF can increase exposure to afatinib *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

Concomitant taking of P-gp inducers (including but not limited to rifampicin, carbamazepine, phenytoin, phenobarbital, and St. John's wort) with GILOTRIF can decrease exposure to afatinib *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Based on findings from animal studies and its mechanism of action, GILOTRIF can cause fetal harm when administered to a pregnant woman. There are no available data on the use of GILOTRIF in pregnant women. Administration of afatinib to pregnant rabbits during organogenesis at exposures approximately 0.2 times the exposure in humans at the recommended dose of 40 mg daily resulted in embryotoxicity and, in rabbits showing maternal toxicity, increased abortions at late gestational stages *[see Data]*. Advise a pregnant woman of the potential risk to a fetus.

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

Data

Animal Data
In an embryo-fetal development study in rabbits, administration of afatinib to pregnant animals at doses of 5 mg/kg (approximately 0.2 times the exposure by AUC at the recommended human dose of 40 mg daily) or greater during the period of organogenesis caused increased post-implantation loss, and in animals showing maternal toxicity, abortion at late gestational stages. In the same study, at the high dose level of 10 mg/kg (approximately 0.7 times the exposure by AUC at the recommended human dose of 40 mg daily), there were reduced fetal weights, and increases in the incidence of runts, as well as visceral and dermal variations. In an embryo-fetal development study in rats, there were skeletal alterations consisting of incomplete or delayed ossifications and reduced fetal weight at a dose of 16 mg/kg (approximately twice the exposure based on AUC at the recommended human dose of 40 mg daily).

8.2 Lactation

Risk Summary

There are no data on the presence of afatinib in human milk or its effects on the breastfed infant or on milk production. Afatinib was present in the milk of lactating rats *[see Data]*. Because of the potential for serious adverse reactions in nursing infants from GILOTRIF, advise a lactating woman not to

breastfeed during treatment with GILOTRIF and for 2 weeks after the final dose.

Data

Afatinib was present in the milk of lactating rats at concentrations 80 and 150 times higher than those found in plasma at 1 and 6 hours after administration.

8.3 Females and Males of Reproductive Potential

Contraception

Females

GILOTRIF can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with GILOTRIF, and for at least 2 weeks after the last dose of GILOTRIF *[see Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)]*.

Infertility

Based on results from an animal fertility study, GILOTRIF may reduce fertility in females and males of reproductive potential. It is not known if the effects on fertility are reversible *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness of GILOTRIF in pediatric patients have not been established.

8.5 Geriatric Use

Study 1 did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

In Study 2, 53% of the 398 patients randomized to receive afatinib were 65 years of age or older and 11% were 75 years or older. In an exploratory subgroup analysis of Study 2, the hazard ratio for overall survival in patients less than 65 years old was 0.68 (95% CI: 0.55, 0.85) and in patients 65 years or older was 0.95 (95% CI: 0.76, 1.19). No overall differences in safety were observed between patients 65 years and older and younger patients.

8.6 Renal Impairment

Patients with severe renal impairment have a higher exposure to afatinib than patients with normal renal function. Administer GILOTRIF at a starting dose of 30 mg once daily in patients with severe renal impairment. Adjustments to the starting dose of GILOTRIF are not necessary in patients with mild or moderate renal impairment. Dosing recommendations for patients with eGFR <15 mL/min/1.73 m^2 or on dialysis cannot be provided as GILOTRIF has not been studied in these patient populations *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

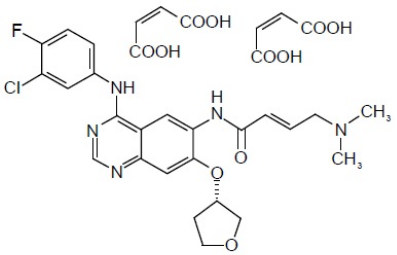
GILOTRIF has not been studied in patients with severe (Child Pugh C) hepatic impairment. Adjustments to the starting dose of GILOTRIF are not necessary in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. Closely monitor patients with severe hepatic impairment and adjust GILOTRIF dose if not tolerated *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Overdose was reported in 2 healthy adolescents each of whom ingested 360 mg of GILOTRIF (as part of a mixed-drug ingestion) resulting in nausea, vomiting, asthenia, dizziness, headache, abdominal pain, and elevated amylase [<1.5 times upper limit of normal (ULN)]. Both subjects recovered.

11 DESCRIPTION

GILOTRIF tablets contain afatinib, a tyrosine kinase inhibitor which is a 4-anilinoquinazoline. Afatinib is presented as the dimaleate salt, with the chemical name 2-butenamide, *N*-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3*S*)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(dimethylamino)-,(2*E*)-, (2*Z*)-2-butenedioate (1:2). Its structural formula is:



Afatinib dimaleate is a white to brownish yellow powder, water soluble and hygroscopic, with an empirical formula of $C_{32}H_{33}ClFN_5O_{11}$, and a molecular weight of 718.1 g/mol.

GILOTRIF tablets for oral administration are available in 40 mg, 30 mg, or 20 mg of afatinib (equivalent to 59.12 mg, 44.34 mg, or 29.56 mg afatinib dimaleate, respectively). The inactive ingredients of GILOTRIF are the following: Tablet Core: lactose monohydrate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate and Coating: hypromellose, polyethylene glycol, titanium dioxide, talc, polysorbate 80, FD&C Blue No. 2 (40 mg and 30 mg tablets only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Afatinib covalently binds to the kinase domains of EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4) and irreversibly inhibits tyrosine kinase autophosphorylation, resulting in downregulation of ErbB signaling.

Afatinib demonstrated inhibition of autophosphorylation and *in vitro* proliferation of cell lines expressing wild-type EGFR or those expressing selected EGFR exon 19 deletion mutations or exon 21 L858R mutations, including some with a secondary T790M mutation, at afatinib concentrations achieved, at least transiently, in patients. In addition, afatinib inhibited *in vitro* proliferation of cell lines overexpressing HER2.

Treatment with afatinib resulted in inhibition of tumor growth in nude mice implanted with tumors either overexpressing wild type EGFR or HER2 or in an EGFR L858R/T790M double mutant model.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of multiple doses of GILOTRIF (50 mg once daily) on the QTc interval was evaluated in an open-label, single-arm study in patients with relapsed or refractory solid tumors. No large changes in the mean QTc interval (i.e., >20 ms) were detected in the study.

12.3 Pharmacokinetics

Absorption and Distribution
Following oral administration of GILOTRIF tablets, time to peak afatinib plasma concentrations (T_{max}) is 2 to 5 hours. Maximum concentration (C_{max}) and area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) values increased slightly more than dose proportional in the range of 20 to 50 mg. The geometric mean relative bioavailability of 20 mg GILOTRIF tablets was 92% as compared to an oral solution. *In vitro* binding of afatinib to human plasma proteins is approximately 95%.

A high-fat meal decreased C_{max} by 50% and $AUC_{0-\infty}$ by 39% relative to the fasted condition *[see Dosage and Administration (2.2)]*.

Metabolism and Elimination
Covalent adducts to proteins are the major circulating metabolites of afatinib and enzymatic metabolism of afatinib is minimal.

In humans, excretion of afatinib is primarily *via* the feces (85%) with 4% recovered in the urine following a single oral dose of [^{14}C]-labeled afatinib solution. The parent compound accounted for 88% of the recovered dose.

The elimination half-life of afatinib is 37 hours after repeat dosing in cancer patients. Steady-state plasma concentrations are achieved within 8 days of repeat dosing of GILOTRIF resulting in an accumulation of 2.8-fold for AUC and 2.1-fold for C_{max}.

Specific Populations
Renal Impairment: A pharmacokinetic study was conducted in 14 subjects with normal (eGFR ≥90 mL/min/1.73 m^2) renal function, 8 subjects with moderate (eGFR=30 to 59 mL/min/1.73 m^2) and 8 subjects with severe (eGFR=15 to 29 mL/min /1.73 m^2) renal impairment. All subjects received a single 40 mg oral dose of GILOTRIF. The geometric mean AUC_{inf} for afatinib was 50% higher in subjects with severe renal impairment and was 22% higher in subjects with moderate renal impairment as compared to subjects with normal renal function. Geometric mean C_{max} was 22% higher in subjects with severe renal impairment and was comparable in subjects with moderate renal impairment as compared to subjects with normal renal function *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*. GILOTRIF has not been studied in patients with eGFR <15 mL/min/1.73 m^2 or on dialysis.

Hepatic Impairment: Afatinib is eliminated mainly by biliary/fecal excretion. Mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment had no influence on the afatinib exposure following a single dose of GILOTRIF. Subjects with severe (Child Pugh C) hepatic dysfunction have not been studied *[see Use in Specific Populations (8.7)]*.

Body Weight, Gender, Age, and Race: Based on the population pharmacokinetic analysis, weight, gender, age, and race do not have a clinically important effect on exposure of afatinib.

Drug Interactions
Effect of P-gp Inhibitors and Inducers on Afatinib: The effect of ritonavir dosing time relative to a single oral dose of GILOTRIF was evaluated in healthy subjects taking 40 mg of GILOTRIF alone as compared to those after ritonavir (200 mg twice daily for 3 days) co-administration at 6 hours after GILOTRIF administration. The relative bioavailability for $AUC_{0-\infty}$ and C_{max} of afatinib was 119% and 104% when co-administered with ritonavir, and 111% and 105% when ritonavir was administered 6 hours after taking GILOTRIF. In another study, when ritonavir (200 mg twice daily for 3 days) was administered 1 hour before a 20 mg single dose of GILOTRIF, exposure to afatinib increased by 48% for $AUC_{0-\infty}$ and 39% for C_{max} *[see Drug Interactions (7)]*.

Pre-treatment with a potent inducer of P-gp, rifampicin (600 mg once daily for 7 days) decreased the plasma exposure to afatinib by 34% ($AUC_{0-\infty}$) and 22% (C_{max}) *[see Drug Interactions (7)]*.

P-glycoprotein (P-gp): Based on *in vitro* data, afatinib is a substrate and an inhibitor of P-gp.

Breast Cancer Resistance Protein (BCRP): Based on *in vitro* data, afatinib is a substrate and an inhibitor of the transporter BCRP.

Effect of CYP450 Enzyme Inducers and Inhibitors on Afatinib: *In vitro* data indicated that drug-drug interactions with GILOTRIF due to inhibition or induction of CYP450 enzymes by concomitant medications are unlikely. The metabolites formed by CYP450-dependent reactions were approximately 9% of the total metabolic turnover in sandwich-cultured human hepatocytes. In humans, enzyme-catalyzed metabolic reactions play a negligible role for the metabolism of afatinib. Approximately 2% of the afatinib dose was metabolized by FMO3; the CYP3A4-dependent N-demethylation was not detected.

Effect of Afatinib on CYP450 Enzymes: Afatinib is not an inhibitor or an inducer of CYP450 enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, and 3A4) in cultured primary human hepatocytes. Therefore, afatinib is unlikely to affect the metabolism of other drugs that are substrates of CYP450 enzymes.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with afatinib.

A marginal response to afatinib was observed in a single tester strain of a bacterial (Ames) mutagenicity assay. No mutagenic or genotoxic potential was identified in an *in vitro* chromosomal aberration test at non-cytotoxic concentrations as well as in the *in vivo* bone marrow micronucleus assay, the *in vivo* Comet assay, and an *in vivo* 4-week oral mutation study in the Muta™ Mouse.

In a dedicated fertility study, male and female rats received afatinib daily by oral administration at doses of 4, 6, or 8 mg/kg. In males at doses of 6 mg/kg (approximately equal to the exposure by AUC in patients at the recommended human dose of 40 mg daily) or greater, there was an increase in the incidence of low or no sperm count, though overall fertility was not affected; decreases in sperm count were supported by findings of increased apoptosis in the testes and atrophy in the seminal vesicles and the prostate in general toxicology studies. In females at the high dose of 8 mg/kg (approximately 0.63 times the exposure by AUC in patients at the recommended human dose of 40 mg daily), there was a mild decrease in the number of corpora lutea along with a mild increase in post-implantation loss due to early resorptions. In a 4-week general toxicology study, female rats had decreases in ovarian weights at all dose levels; organ weight had not fully recovered by the end of a 2-week recovery period.

14 CLINICAL STUDIES

14.1 EGFR Mutation-Positive Non-Small Cell Lung Cancer

The efficacy and safety of GILOTRIF in the first-line treatment of 345 patients with EGFR mutation-positive, metastatic [Stage IV and Stage IIIb with pleural and/or pericardial effusion as classified by the American Joint Commission on Cancer (AJCC, 6th edition)] non-small cell lung cancer (NSCLC) were established in a randomized, multicenter, open-label trial (Study 1). Patients were randomized (2:1) to receive GILOTRIF 40 mg orally once daily (n=230) or up to 6 cycles of pemetrexed/cisplatin (n=115). Randomization was stratified according to EGFR mutation status (exon 19 deletion vs exon 21 L858R vs other) and race (Asian vs non-Asian). The major efficacy outcome was progression-free survival (PFS) as assessed by an independent review committee (IRC). Other efficacy outcomes included overall response rate (ORR) and overall survival (OS). EGFR mutation status was prospectively determined for screening and enrollment of patients by a clinical trial assay (CTA). Tumor samples from 264 patients (178 randomized to GILOTRIF and 86 patients randomized to chemotherapy) were tested retrospectively by the companion diagnostic *therascreen*® EGFR RGQ PCR Kit, which is FDA-

approved for selection of patients for GILOTRIF treatment.

Among the patients randomized, 65% were female, median age was 61 years, baseline ECOG performance status was 0 (39%) or 1 (61%), 26% were Caucasian and 72% were Asian. The majority of the patients had a tumor sample with an EGFR mutation categorized by the CTA as either exon 19 deletion (49%) or exon 21 L858R substitution (40%), while the remaining 11% had other mutations.

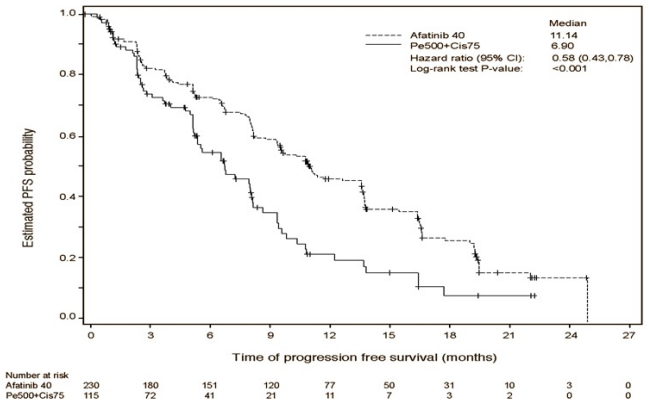
A statistically significant improvement in PFS as determined by the IRC was demonstrated for patients randomized to GILOTRIF compared with those randomized to chemotherapy. See Table 5 and Figure 1. There was no statistically significant difference for overall survival between the treatment arms at the final pre-planned analysis.

Table 5 Efficacy Results

	GILOTRIF (N=230)	Pemetrexed/Cisplatin (N=115)
Progression-Free Survival by IRC		
Number of Deaths or Progressions, N (%)	152 (66.1%)	69 (60.0%)
Median Progression-Free Survival (months)	11.1	6.9
95% CI	(9.6, 13.6)	(5.4, 8.2)
HR (95% CI)	0.58 (0.43, 0.78)	
Stratified Log-Rank Test p-value*	<0.001	
Overall Survival		
Number of Deaths, N (%)	140 (60.9%)	73 (63.5%)
Median Overall Survival (months)	28.2	28.2
95% CI	(24.6, 33.6)	(20.7, 33.2)
HR (95% CI)	0.88 (0.66, 1.17)	
Stratified Log-Rank Test p-value*	0.39	
Overall Response Rate (CR + PR) by IRC		
N (%)	116 (50.4%)	22 (19.1%)
Response Duration		
Median (months)	12.5	6.7

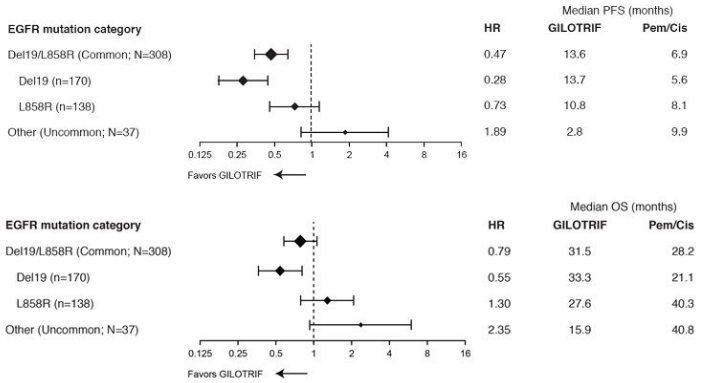
*Stratified by EGFR mutation status and race.
HR=hazard ratio; CR=complete response; PR=partial response

Figure 1 Kaplan-Meier Curve for PFS by Independent Review by Treatment Group



Subgroup analyses were conducted based on the stratification factor of EGFR mutation status (Del19, L858R, other) and mutation category (common [Del19, L858R] vs uncommon [other]). See Figure 2.

Figure 2 Forest Plot of PFS and OS for Common (Del19, L858R) and Uncommon (other) EGFR Mutation Categories



There were 26 GILOTRIF-treated patients in the “other” (uncommon) EGFR mutations subgroup with nine unique mutation patterns. None of these 26 patients achieved a complete response, while four achieved a partial response (see Table 6 below). No responses were seen in GILOTRIF-treated patients with the following mutations: T790M alone (n=2), deletion 19 and T790M (n=3), G719X and T790M (n=1), exon 20 insertion (n=6), and L861Q alone (n=3). There were 11 chemotherapy-treated patients in the “other” uncommon EGFR mutation subgroup; of these, four (36%) achieved a partial response.

Table 6 Objective Tumor Responses in GILOTRIF-Treated Patients Based on Investigator Assessment in the “Other” (Uncommon) EGFR Mutation Subgroup

EGFR Mutations	Number of GILOTRIF-Treated Patients	Number of Patients with Partial Responses	Duration of Response
L858R	5	1	6.9 months

and T790M	5	1	6.9 months
L858R and S768I	2	1	12.4+ months
S768I	1	1	16.5+ months
G719X	3	1	9.6 months

+ Censored observation

14.2 Previously Treated, Metastatic Squamous NSCLC

The efficacy and safety of GILOTRIF were demonstrated in a randomized, multicenter, open-label, active-controlled study (Study 2). Patients were required to have histologically documented, metastatic squamous NSCLC and have experienced disease progression following an adequate course (≥ 4 cycles) of a platinum-based doublet chemotherapy regimen. Patients were randomized (1:1) to receive GILOTRIF 40 mg or erlotinib 150 mg orally once daily until progression. Randomization was stratified by region (Eastern Asia vs other). The major efficacy outcome measure was PFS as assessed by an independent review committee (IRC) using RECIST v 1.1. Additonal efficacy outcome measures were OS and ORR as assessed by IRC.

Baseline patient demographics of the 795 patients were: median age 64 years (range: 35 to 88); 73% White; 24% Asian; 84% male; 33% ECOG performance status (PS) 0 and 67% ECOG PS 1; and 95% current or former smokers. With regard to tumor characteristics, 96% had squamous cell histology and 3.5% had mixed cell histology. All patients received platinum-based doublet therapy.

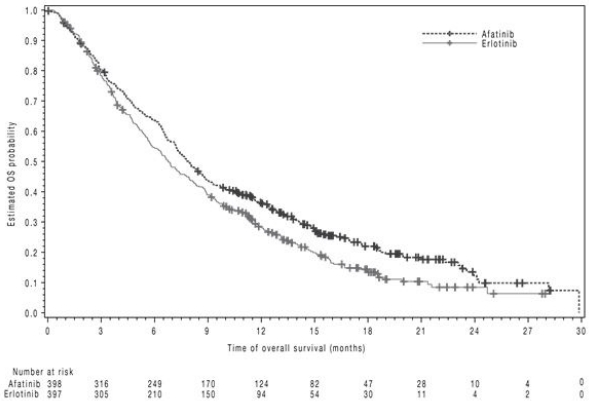
The study demonstrated a statistically significant improvement in PFS and OS for patients randomized to GILOTRIF as compared with erlotinib (see Table 7 and Figure 3).

Table 7 Efficacy Results

	GILOTRIF	**Erlotinib**
Overall Survival		
	N=398	N=397
Number of Deaths, N (%)	307 (77%)	325 (82%)
Median overall survival (months)	7.9	6.8
95% CI	(7.2, 8.7)	(5.9, 7.8)
HR (95% CI)	0.81 (0.69, 0.95)	
p-value*	0.008	
Progression-Free Survival (PFS) by IRC		
	N=335	N=334
Number of Events, N (%)	202 (60%)	212 (64%)
Median PFS (months)	2.4	1.9
95% CI	(1.9, 2.9)	(1.9, 2.2)
HR (95% CI)	0.82 (0.68, 0.998)	
p-value*	0.0427	
Overall Response Rate (ORR) by IRC		
	N=335	N=334
ORR	3%	2%
(95% CI)	(1.7, 5.8)	(0.8, 4.3)

*Log-rank test stratified by region.
HR=hazard ratio

Figure 3 Kaplan-Meier Curves of Overall Survival



16 HOW SUPPLIED/STORAGE AND HANDLING

GILOTRIF tablets are available as follows:

40 mg: light blue, film-coated, round, biconvex, bevel-edged tablets debossed with “T40” on one side and the Boehringer Ingelheim company symbol on the other side.
Unit of use bottles of 30 NDC: 0597-0138-30

30 mg: dark blue, film-coated, round, biconvex, bevel-edged tablets debossed with “T30” on one side and the Boehringer Ingelheim company symbol on the other side.
Unit of use bottles of 30 NDC: 0597-0137-30

20 mg: white to slightly yellowish, film-coated, round, biconvex, bevel-edged tablets debossed with “T20” on one side and the Boehringer Ingelheim company symbol on the other side.
Unit of use bottles of 30 NDC: 0597-0141-30

Storage
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Dispense medication in the original container to protect from exposure to high humidity and light.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Diarrhea
Advise patients that diarrhea occurs in nearly all patients who receive GILOTRIF. Inform patients that diarrhea may result in dehydration and renal impairment if not treated. Advise patients to notify their physician if diarrhea develops and to seek medical attention promptly for severe or persistent diarrhea *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].*

Bullous and Exfoliative Skin Disorders
Advise patients to minimize sun exposure with protective clothing and use of sunscreen while taking GILOTRIF *[see Warnings and Precautions (5.2)]*.

Interstitial Lung Disease
Advise patients to immediately report any new or worsening lung symptoms, or any combination of the following symptoms: trouble breathing or shortness of breath, cough, fever *[see Warnings and Precautions (5.3)]*.

Hepatic Toxicity
Advise patients that they will need to undergo liver function monitoring periodically. Advise patients to immediately report any symptoms of a liver problem [e.g., skin or the whites of eyes turn yellow, urine turns dark or brown (tea colored), pain on the right side of stomach, bleeds or bruises more easily than normal, lethargy] *[see Warnings and Precautions (5.4)]*.

Keratitis
Advise patients to immediately report eye problems (e.g., eye pain, swelling, redness, blurred vision, or other vision changes) *[see Warnings and Precautions (5.5)]*.

Left Ventricular Dysfunction
Advise patients to contact a healthcare professional immediately for any of the following: new onset or worsening shortness of breath or exercise intolerance, cough, fatigue, swelling of the ankles/legs, palpitations, or sudden weight gain *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)]*.

Instructions for Taking GILOTRIF
Advise patients to take GILOTRIF on an empty stomach at least 1 hour before or 2 hours after eating *[see Dosage and Administration (2.2)]*. Advise patients not to take a missed dose within 12 hours of the next dose.

Embryo-Fetal Toxicity
Advise pregnant women and females of reproductive potential that GILOTRIF can result in fetal harm. Advise female patients to contact their healthcare provider with a known or suspected pregnancy. Advise females of reproductive potential to use effective contraception during treatment with GILOTRIF and for at least 2 weeks after the last dose of GILOTRIF *[see Use in Specific Populations (8.1, 8.3)]*.

Lactation
Advise women not to breastfeed during treatment with GILOTRIF and for 2 weeks after the last dose of GILOTRIF *[see Use in Specific Populations (8.2)]*.

Infertility
Advise females and males of reproductive potential of the potential for reduced fertility from GILOTRIF *[see Use in Specific Populations (8.3)]*.

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Ridgefield, CT 06877 USA

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IT5562OD242016

Patient Information
GILOTRIF® (JEE-loh-trif)
(afatinib) tablets

What is GILOTRIF?
GILOTRIF is a prescription medicine used to treat non-small cell lung cancer (NSCLC):

- that has certain types of abnormal epidermal growth factor receptor (EGFR) genes. Your doctor will perform a test to check for certain types of abnormal EGFR genes, and make sure that GILOTRIF is right for you. GILOTRIF may be used when you have not had previous treatment for cancer that has spread to other parts of your body. It is not known if GILOTRIF is safe and effective in treating lung cancer with other abnormal EGFR genes.

  or
- that is squamous type and has spread to other parts of the body after you have tried chemotherapy that contains platinum.

It is not known if GILOTRIF is safe and effective in children.

Before you take GILOTRIF, tell your doctor about all of your medical conditions, including if you:

- have kidney or liver problems
- have lung or breathing problems other than lung cancer
- have a history of severe dry eye or any other eye problems. Tell your doctor if you wear contact lenses.
- have heart problems
- are pregnant or plan to become pregnant. GILOTRIF can harm your unborn baby. You should not become pregnant while taking GILOTRIF.
  - Women who are able to become pregnant should use effective birth control during treatment with GILOTRIF and for at least 2 weeks after your last dose of GILOTRIF. Talk to your doctor about birth control methods that may be right for you.
  - Tell your doctor right away if you become pregnant or think you are pregnant while taking GILOTRIF.
- are breastfeeding or plan to breastfeed. It is not known if GILOTRIF passes into your breast milk. Do not breastfeed while taking GILOTRIF and for 2 weeks after your last dose of GILOTRIF. Talk to your doctor about the best way to feed your baby if you take GILOTRIF.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. GILOTRIF may affect the way other medicines work, and other medicines may affect the way GILOTRIF works.
Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine.

How should I take GILOTRIF?

- Take GILOTRIF exactly as your doctor tells you to take it.
- Your doctor will tell you how many GILOTRIF tablets to take and when to take them. Do not change your dose or stop GILOTRIF unless your doctor tells you to.
- Take GILOTRIF on an empty stomach at least 1 hour before a meal or 2 hours after a meal.
- If you miss a dose of GILOTRIF, take it as soon as you remember. If it is within 12 hours of your next dose, skip the dose and just take your next dose at your regular time. Do not take 2 doses of GILOTRIF at the same time.
- If you take too much GILOTRIF, call your doctor or go to the nearest hospital emergency room right away.

What should I avoid while taking GILOTRIF?

Limit your time in the sun. GILOTRIF can make your skin sensitive to the sun. You could get or have worsening rash or acne. You could get a severe sunburn. Use sunscreen and wear a hat and clothes that cover your skin while you are taking GILOTRIF if you have to be in sunlight.

What are the possible side effects of GILOTRIF?

GILOTRIF may cause serious side effects, including:

- **diarrhea.** Diarrhea is common with GILOTRIF and may sometimes be severe. Severe diarrhea can cause loss of too much body fluid (dehydration) and kidney problems that can sometimes lead to death. During your treatment with GILOTRIF, your doctor should prescribe medicines to treat diarrhea. Take this medicine exactly as your doctor tells you to. Tell your doctor if you have diarrhea. Get medical attention right away if your diarrhea does not go away or becomes severe.
- **skin reactions.** GILOTRIF can cause redness, rash, and acne. It is important to get treatment for skin reactions as soon as you notice them. Take medicines to help skin reactions exactly as your doctor tells you to. Get medical attention right away if you develop severe skin reactions such as peeling or blistering of the skin, or blisters in your mouth.
- **lung or breathing problems.** Gilotrif may cause inflammation of the lung that may lead to death. Symptoms may be similar to those symptoms from lung cancer. Tell your doctor right away if you have any new or worsening lung problems, or any combination of the following symptoms: trouble breathing or shortness of breath, cough, or fever.
- **liver problems.** Gilotrif can cause liver problems that can sometimes lead to death. Tell your doctor right away if you have any symptoms of a liver problem which may include:
  - yellowing of your skin or the white part of your eyes (jaundice)
  - dark or brown (tea colored) urine
  - pain on the upper right side of your stomach area (abdomen)
  - bleeding or bruising more easily than normal
  - feeling very tired

  Your doctor will do blood tests to check your liver function during your treatment with GILOTRIF.
- **eye problems.** Tell your doctor right away if you have symptoms of eye problems which may include:
  - eye pain, swelling, redness, or tearing
  - blurred vision
  - sensitivity to light
  - other changes in your vision
- **heart problems.** Tell your doctor right away if you have symptoms of a heart problem which may include:
  - new or worsening shortness of breath while at rest or with activity
  - cough
  - tiredness
  - swelling of your ankles, feet, or legs
  - feeling that your heart is pounding or racing (palpitations)
  - sudden weight gain

The most common side effects of GILOTRIF include:

- diarrhea
- rash
- mouth sores
- nail inflammation
- dry skin
- acne
- decreased appetite
- nausea
- vomiting
- itching

GILOTRIF may cause decreased fertility in females and males. Talk to your doctor if you have concerns about fertility.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of GILOTRIF. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store GILOTRIF?

- Store GILOTRIF at room temperature 68°F to 77°F (20°C to 25°C).
- Keep GILOTRIF in the original container and keep the container tightly closed.
- Keep GILOTRIF away from moisture and light.
- Safely throw away (discard) any GILOTRIF that is out of date or no longer needed.

Keep GILOTRIF and all medicines out of the reach of children.

General information about GILOTRIF

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use GILOTRIF for a condition for which it was not prescribed. Do not give GILOTRIF to other people, even if they have the same symptoms you have. It may harm them. You can ask your doctor or pharmacist for information about GILOTRIF that is written for health professionals.

What are the ingredients in GILOTRIF?

Active ingredient: afatinib

Inactive ingredients: Tablet Core: lactose monohydrate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate. **Tablet Coating:** hypromellose, polyethylene glycol, titanium dioxide, talc, polysorbate 80, FD&C Blue No. 2 (40 mg and 30 mg tablets only).

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877 USA
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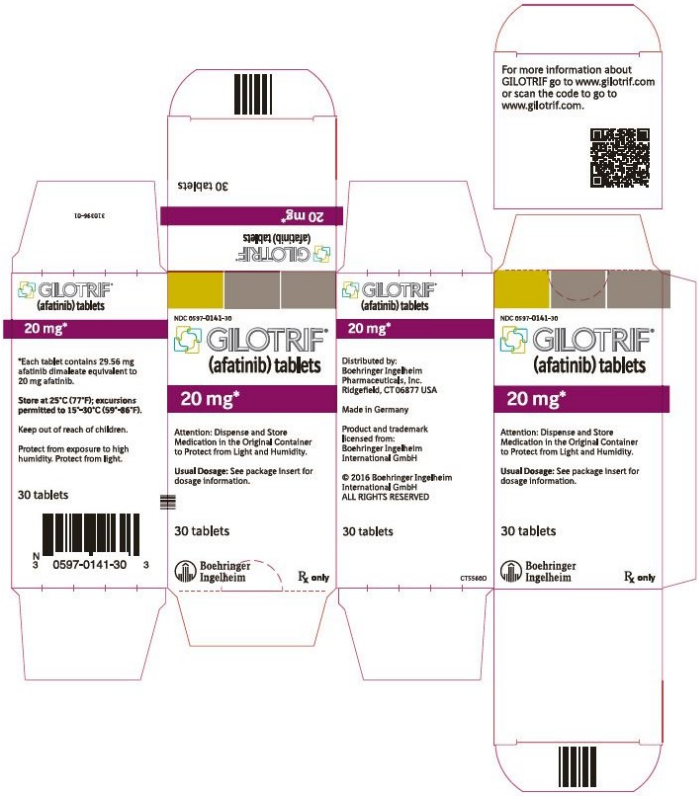
IT5562OD212016

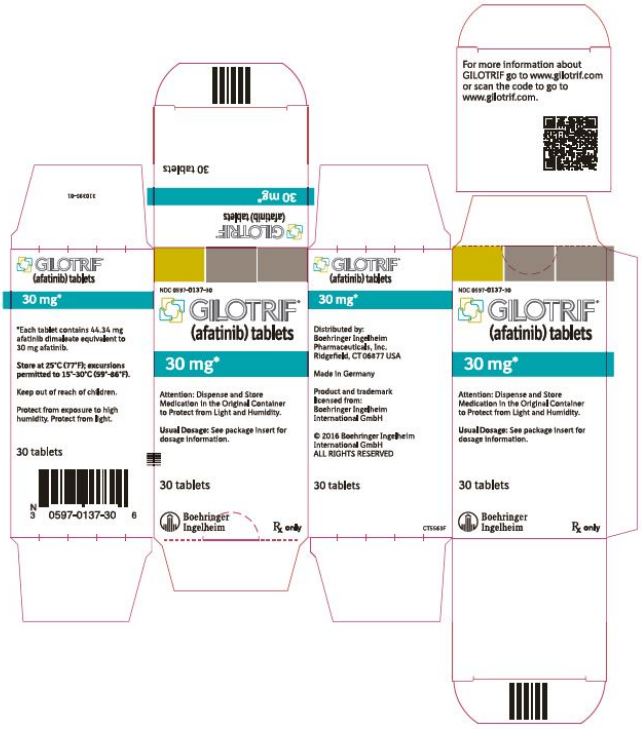
For more information, go to www.gilotrif.com or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or (TTY) 1-800-459-9906, or scan the code to go to www.gilotrif.com.

This Patient Information has been approved by the U.S. Food and Drug Administration.
Revised: April 2016

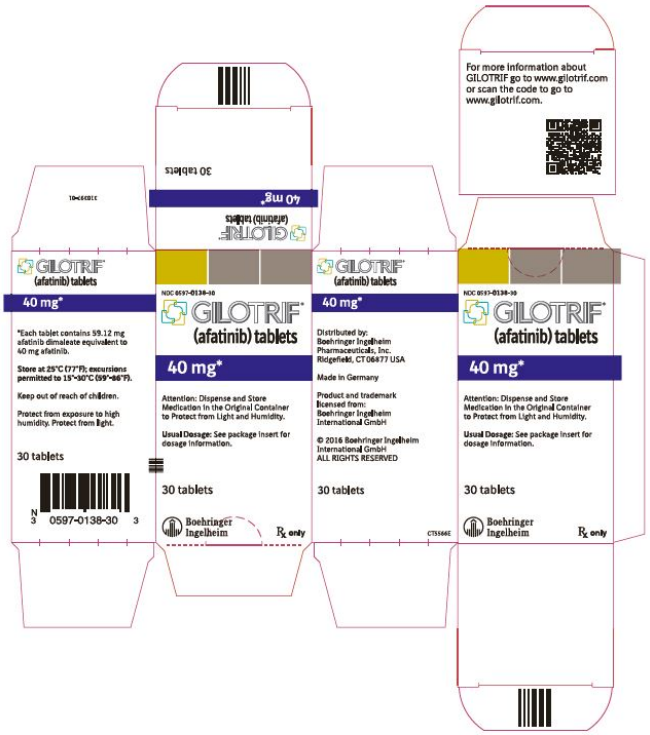
Gilotrif® 20 mg Tablets
NDC: 0597-0141-30



Gilotrif® 30 mg Tablets
NDC: 0597-0137-30



Gilotrif® 40 mg Tablets
NDC: 0597-0138-30



GILOTRIF

afatinib tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0597-0141
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
afatinib (UNII: 41UD74L59M) (afatinib - UNII:41UD74L59M)	afatinib	20 mg

Product Characteristics

Color	WHITE (Slightly yellowish)	**Score**	no score
Shape	ROUND	**Size**	8mm
Flavor		**Imprint Code**	T20
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0597-0141-30	1 in 1 CARTON	08/13/2013	
1		30 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA201292	07/12/2013	

GILOTRIF

afatinib tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0597-0137
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
afatinib (UNII: 41UD74L59M) (afatinib - UNII:41UD74L59M)	afatinib	30 mg

Product Characteristics

Color	BLUE (Dark Blue)	**Score**	no score
Shape	ROUND	**Size**	9mm
Flavor		**Imprint Code**	T30
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0597-0137-30	1 in 1 CARTON	08/09/2013	
1		30 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA201292	07/12/2013	

GILOTRIF

afatinib tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0597-0138
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
afatinib (UNII: 41UD74L59M) (afatinib - UNII:41UD74L59M)	afatinib	40 mg

Product Characteristics

Color	BLUE (Light Blue)	**Score**	no score
Shape	ROUND	**Size**	10mm
Flavor		**Imprint Code**	T40
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0597-0138-30	1 in 1 CARTON	08/08/2013	
1		30 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA201292	07/12/2013	

Labeler - Boehringer Ingelheim Pharmaceuticals, Inc. (603175944)

Registrant - Boehringer Ingelheim Pharmaceuticals, Inc. (603175944)

Establishment

Name	Address	ID/FEI	Business Operations
Boehringer Ingelheim Pharma GmbH and Co. KG		551147440	API MANUFACTURE(0597-0137, 0597-0138, 0597-0141) , MANUFACTURE(0597-0141, 0597-0137, 0597-0138) , ANALYSIS(0597-0141, 0597-0138, 0597-0137) , LABEL(0597-0137, 0597-0138, 0597-0141) , PACK(0597-0138, 0597-0137, 0597-0141)

Establishment

Name	Address	ID/FEI	Business Operations
Boehringer Ingelheim Roxane, Inc.		058839929	LABEL(0597-0137, 0597-0138, 0597-0141) , PACK(0597-0138, 0597-0137, 0597-0141)