

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201292Orig1s000

LABELING

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

INDICATIONS AND USAGE

GILOTRIF is a 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 GILOTRIF have not been established in patients whose tumors have other EGFR mutations (1)

DOSAGE AND ADMINISTRATION

- Recommended dose: 40 mg orally, once daily (2.2)
- Instruct patients to take GILOTRIF at least 1 hour before or 2 hours after a meal (2.2)

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 0.15% 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 1.5% 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 0.18% of patients. Monitor with periodic liver testing. Withhold or discontinue GILOTRIF for severe or worsening liver tests. (2.3, 5.4)
- Keratitis: Occurs in 0.8% of patients. Withhold GILOTRIF for keratitis evaluation. Withhold or discontinue GILOTRIF for confirmed ulcerative keratitis. (2.3, 5.5)
- Embryofetal toxicity: Can cause fetal harm. Advise females of the potential hazard to the fetus and to use highly effective contraception. (5.6)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 20\%$) are diarrhea, rash/dermatitis acneiform, stomatitis, paronychia, dry skin, decreased appetite, 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

- Nursing mothers: Discontinue drug or nursing (8.3)

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

Revised: 07/2013

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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)*].

Limitation of Use: Safety and efficacy of GILOTRIF have not been established in patients whose tumors have other EGFR mutations [see *Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the 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)* and *Clinical Studies (14)*]. 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. 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 Modification

Withhold GILOTRIF for any drug-related 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 dysfunction of Grade 2 or higher

*National Cancer Institute Common Terminology Criteria for Adverse Events, v 3.0

Resume treatment when the adverse reaction fully resolves, returns to baseline, or improves to Grade 1. Reinststitute 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
- Severe or intolerable adverse reaction occurring at a dose of 20 mg per day

P-gp Inhibitors

For patients who require therapy with a P-glycoprotein (P-gp) inhibitor, reduce GILOTRIF daily dose by 10 mg if not tolerated. 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

For patients who require chronic therapy with a P-gp inducer, increase GILOTRIF daily dose by 10 mg as tolerated. 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; some of these cases were fatal. In Study 1, diarrhea occurred in 96% of patients treated with GILOTRIF (n=229), of which 15% was Grade 3 in severity and occurred within the first 6 weeks [*see Adverse Reactions (6.1)*]. Renal impairment as a consequence of diarrhea occurred in 6.1% of patients treated with GILOTRIF, out of which 3 (1.3%) were Grade 3.

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 6 (0.15%) of the 3865 patients who received GILOTRIF across clinical trials [*see Adverse Reactions (6.1)*]. 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%. Discontinue GILOTRIF in patients who develop life-threatening bullous, blistering, or exfoliating lesions [*see Dosage and Administration (2.3)*]. 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)*].

5.3 Interstitial Lung Disease (ILD)

ILD or ILD-like adverse reactions (e.g., lung infiltration, pneumonitis, acute respiratory distress syndrome, or alveolitis allergic) occurred in 1.5% of the 3865 patients who received GILOTRIF across clinical trials; of these, 0.4% were fatal. The incidence of ILD appeared to be higher in patients of Asian ethnicity (2.1%) as

compared to non-Asians (1.2%). In Study 1, the incidence of Grade ≥ 3 ILD was 1.3% and resulted in death in 1% 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 3865 patients who received GILOTRIF across clinical trials, 10.1% had liver test abnormalities, of which 7 (0.18%) were fatal. In Study 1, liver test abnormalities of any grade occurred in 17.5% of the patients treated with GILOTRIF.

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 0.8% of patients treated with GILOTRIF among 3865 patients across clinical trials. Keratitis was reported in 5 (2.2%) patients in Study 1, with Grade 3 in 1 (0.4%). 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 Embryofetal Toxicity

Based on its mechanism of action, GILOTRIF can cause fetal harm when administered to a pregnant woman. Afatinib was embryotoxic and, in animals with maternal toxicity, led to abortions at late gestational stages in rabbits at doses of 5 mg/kg (approximately 0.2 times the human exposure at the recommended dose of 40 mg daily) or greater. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus [see *Use in Specific Populations (8.1)*].

Advise females of reproductive potential to use highly effective contraception during treatment, and for at least 2 weeks after the last dose of GILOTRIF. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking GILOTRIF [see *Use in Specific Populations (8.1 and 8.6)*].

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 safety evaluation of GILOTRIF is based on the data from more than 3800 patients, including 2135 NSCLC patients receiving GILOTRIF monotherapy at or above the recommended dose.

Controlled Study

The data in Tables 1 and 2 below reflect exposure of 229 EGFR-TKI 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/m² followed after 30 minutes by cisplatin 75 mg/m² every three weeks for a maximum of six treatment courses.

The median exposure was 11.0 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).

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/Dermatitis acneiform ²	90	16	11	0
Pruritus	21	0	1	0
Dry skin	31	0	2	0
Infections and infestations				
Paronychia ³	58	11	0	0
Cystitis	13	1	5	0
Metabolism and nutrition disorders				
Decreased appetite	29	4	55	4
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

*None of the adverse reactions in this table were Grade 4 in severity

¹Includes stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration

²Includes group of rash preferred terms, acne, acne pustular, dermatitis acneiform

³Includes paronychia, nail infection, nail bed infection

Table 2 Adverse Reactions of Laboratory Abnormalities from the Investigations SOC Reported in ≥5% of GILOTRIF-Treated Patients in Study 1

Adverse Reaction	GILOTRIF n=229		Pemetrexed/Cisplatin n=111	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Alanine aminotransferase increased	11	2	4	0
Hypokalemia ¹	11	4	5	4
Aspartate aminotransferase increased	8	2	2	1

¹Includes hypokalemia, blood potassium decreased

SOC=system organ class

7 DRUG INTERACTIONS

Effect of P-glycoprotein (P-gp) Inhibitors and Inducers

Oral administration of a P-gp inhibitor (ritonavir at 200 mg twice daily) 1 hour before administration of GILOTRIF increased systemic exposure to afatinib by 48%. There was no change in afatinib exposure when ritonavir was administered simultaneously with or 6 hours after GILOTRIF. 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)*].

Co-administration with oral dose of a P-gp inducer (rifampicin at 600 mg once daily for 7 days) decreased exposure to afatinib by 34%. 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

Pregnancy Category D

Risk Summary

Based on its mechanism of action, GILOTRIF can cause fetal harm when administered to a pregnant woman. Afatinib was embryotoxic and, in animals with maternal toxicity, led to abortions at late gestational stages in rabbits 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. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus [see *Warnings and Precautions (5.6)*].

Animal Data

Administration of afatinib to pregnant rabbits 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 embryofetal 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 at the recommended human dose of 40 mg daily).

8.3 Nursing Mothers

It is not known whether afatinib is present in human milk. Afatinib was present in the milk of lactating rats at concentrations 80-150 times higher than those found in plasma from 1 to 6 hours after administration. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from GILOTRIF, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 3865 patients in the clinical studies of GILOTRIF, 32% of patients were 65 years and older, while 7% were 75 years and older. No overall differences in safety were observed between patients 65 years and over and younger patients. In Study 1, 39% of the 345 patients were 65 years of age or older and 4% were 75 years or older. No overall differences in effectiveness were observed between patients 65 years and older and younger patients.

8.6 Females and Males of Reproductive Potential

Contraception

Females

Counsel patients on pregnancy planning and prevention. Advise female patients of reproductive potential to use highly effective contraception during treatment with GILOTRIF, and for at least 2 weeks after the last dose of

GILOTRIF. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking GILOTRIF [see *Use in Specific Populations (8.1)*].

8.7 Renal Impairment

GILOTRIF has not been studied in patients with severely impaired renal function (creatinine clearance [CLcr] <30 mL/min). Adjustments to the starting dose of GILOTRIF are not considered necessary in patients with mild (CLcr 60-89 mL/min) renal impairment. Closely monitor patients with moderate (CLcr 30-59 mL/min) to severe (CLcr <30 mL/min) renal impairment and adjust GILOTRIF dose if not tolerated [see *Clinical Pharmacology (12.3)*].

8.8 Hepatic Impairment

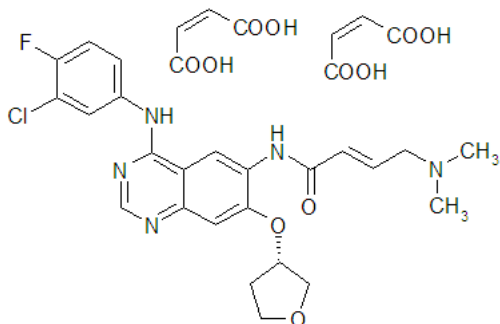
GILOTRIF has not been studied in patients with severe (Child Pugh C) hepatic impairment. Adjustments to the starting dose of GILOTRIF are not considered necessary in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. Closely monitor patients with severe hepatic impairment and adjust GILOTRIF dose if not tolerated [see *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-quinazoliny]-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 C₃₂H₃₃ClFN₅O₁₁, 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. 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: The median trough afatinib plasma concentrations in patients with mild (CLcr 60-89 mL/min) and moderate (CLcr 30-59 mL/min) renal impairment were 27% and 85% higher than those in patients with normal renal function (CLcr \geq 90 mL/min). GILOTRIF has not been studied in patients with severely impaired renal function (CLcr <30 mL/min) [*see Use in Specific Populations (8.7)*].

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 (8.8)].

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-∞} 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-∞} 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-∞}) 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 MutaTM 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

Non-small Cell Lung Cancer (NSCLC)

Study 1

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]) 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 objective 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, the median age was 61 years, the 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.

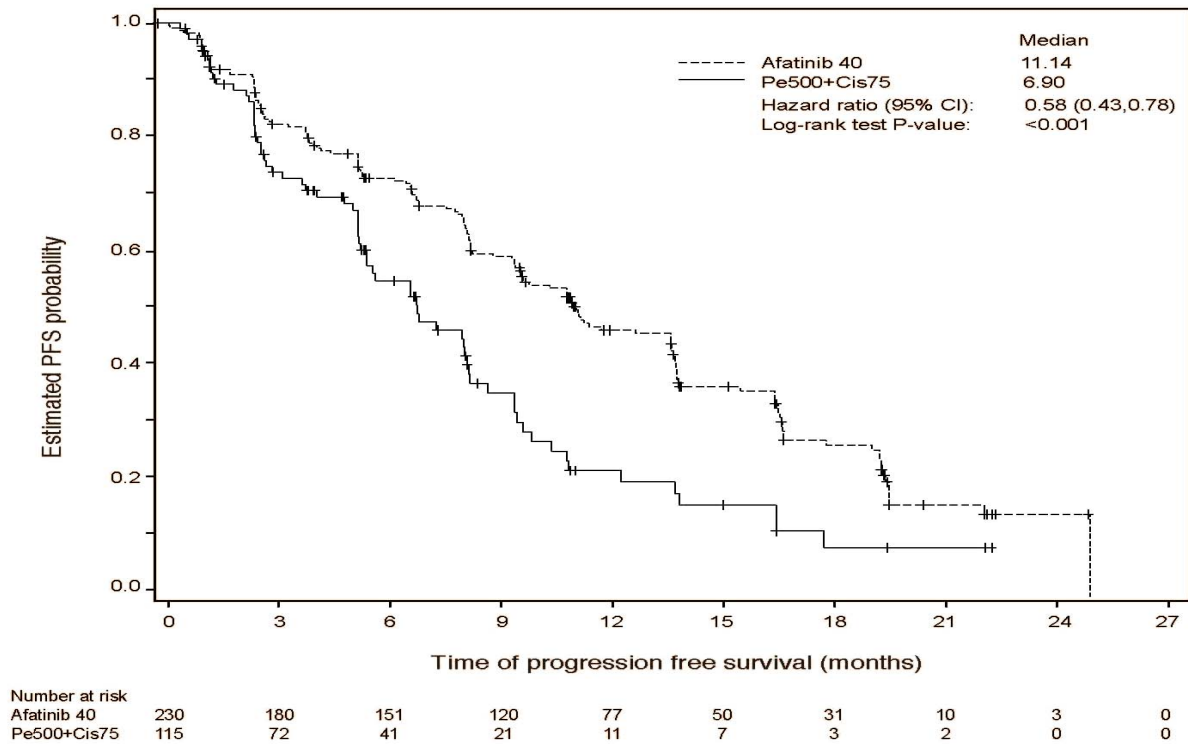
A statistically significant improvement in PFS as determined by the IRC was demonstrated for patients randomized to GILOTRIF compared with those randomized to chemotherapy. See Table 3 and Figure 1. There was no statistically significant difference for overall survival between the treatment arms at the interim analysis conducted at 84% of the planned events for the final analysis.

Table 3: Efficacy Results of Study 1

	GILOTRIF (N=230)	Pemetrexed/Cisplatin (N=115)
Progression-free Survival		
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 (%)	116 (50.4%)	59 (51.2%)
Median Overall Survival (months)	28.1	28.2
95% CI	(24.6, 33.0)	(20.7, 33.2)
HR (95% CI)	0.91 (0.66, 1.25)	
Stratified Log-Rank Test P-value*	0.55	
Objective Response Rate (CR + PR)		
N (%)	116 (50.4%)	22 (19.1%)
Response Duration		
Median (months)	12.5	6.7

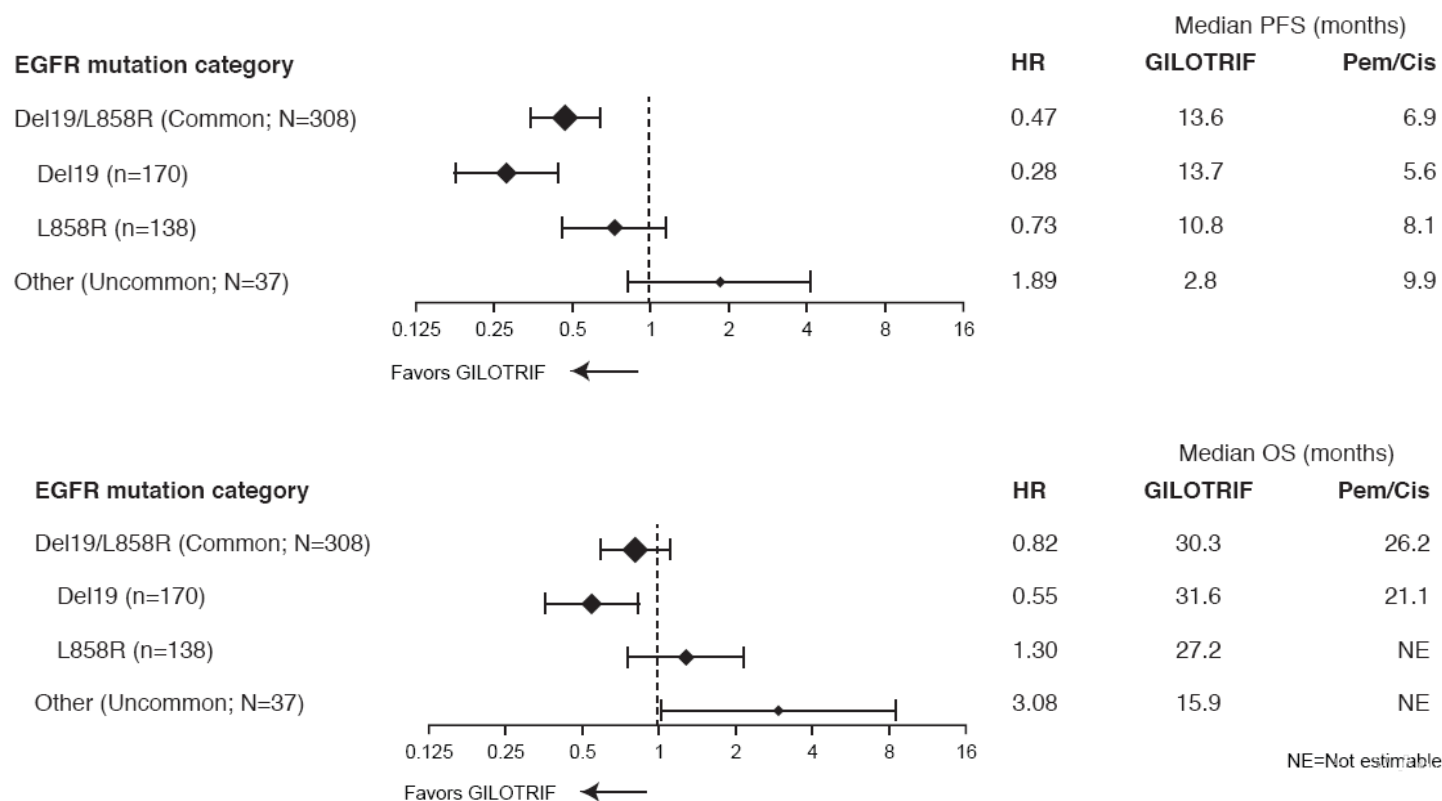
*Stratified by EGFR mutation status and race.
CR=complete response; PR=partial response

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 4 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 4 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 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

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

See 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, bleed or bruise 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.

- **Embryofetal Toxicity**

Counsel patients on pregnancy planning and prevention. Advise females of reproductive potential to use highly effective contraception during treatment, and for at least 2 weeks after taking the last dose of GILOTRIF [*see Warnings and Precautions (5.6) and Use in Specific Populations (8.1)*].

- **Nursing Mothers**

Advise patients to discontinue nursing while taking GILOTRIF [*see Use in Specific Populations (8.3)*].

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Ridgefield, CT 06877 USA

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Patient Information

GILOTRIF™ (JEE-loh-trif) (afatinib) tablets

Read this Patient Information before you start taking GILOTRIF and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or treatment.

What is GILOTRIF?

GILOTRIF is a prescription medicine used to treat people with non-small cell lung cancer (NSCLC),

- that has certain types of abnormal epidermal growth factor receptor (EGFR) genes, and
- who have not had previous treatment for cancer that has spread to other parts of the body

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

What should I tell my doctor before taking GILOTRIF?

Before you take GILOTRIF, tell your doctor 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
- have any other medical conditions
- 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 while taking GILOTRIF.
- are breastfeeding or plan to breastfeed. It is not known if GILOTRIF passes into your breast milk. You and your doctor should decide if you will take GILOTRIF or breastfeed. You should not do both.

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 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.
- **lung or breathing problems.** 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
 - fever
- **liver problems.** 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 infection
- dry skin
- acne
- decreased appetite
- itching

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 between 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.

This Patient Information summarizes the most important information about GILOTRIF. If you would like more information about GILOTRIF, talk with your doctor. You can ask your doctor or pharmacist for information about GILOTRIF that is written for health professionals.

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 below to go to www.gilotrif.com.



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).

This Patient Information has been approved by the U.S. Food and Drug Administration.

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/s/

RICHARD PAZDUR
07/12/2013