### Gilotrif® (afatinib) Distribution Quick Reference Card*

**Access & Clinical Support Services for Patients**

<table>
<thead>
<tr>
<th>Solutions Plus*</th>
<th>Telephone</th>
<th>Fax</th>
<th>Website/Email</th>
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<tbody>
<tr>
<td></td>
<td>1 (877) 814-3915</td>
<td>1 (866) 240-4556</td>
<td>bisolutionsplus.com**</td>
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**Specialty Pharmacy**

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<thead>
<tr>
<th>Specialty Pharmacy</th>
<th>Telephone</th>
<th>Fax</th>
<th>Website/Email</th>
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<tbody>
<tr>
<td>Accredo Health Group</td>
<td>1 (877) 732-3431</td>
<td>1 (888) 454-8488</td>
<td><a href="http://www.accredo.com">www.accredo.com</a></td>
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### Distribution for Authorized Physician Offices, Regional Outpatient Clinics and NCI Retail Locations

<table>
<thead>
<tr>
<th>Distributor</th>
<th>Telephone</th>
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<tr>
<td>Metro Medical</td>
<td>1 (800) 768-2002</td>
<td>1 (615) 256-4194</td>
<td><a href="http://www.metromedicalorder.com">www.metromedicalorder.com</a></td>
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<tr>
<td>Oncology Supply</td>
<td>1 (800) 633-7555</td>
<td>1 (800) 248-8205</td>
<td><a href="http://www.oncologysupply.com">www.oncologysupply.com</a></td>
</tr>
<tr>
<td>McKesson Specialty Health</td>
<td>1 (800) 482-6700</td>
<td>1 (800) 800-5673</td>
<td><a href="http://www.mckesson.com">www.mckesson.com</a></td>
</tr>
<tr>
<td>Cardinal Health Specialty Pharmaceutical Distribution</td>
<td>1 (866) 677-4844</td>
<td>1 (888) 345-4916</td>
<td>specialtyonline.cardinalhealth.com</td>
</tr>
<tr>
<td>HC Pharmacy</td>
<td>1 (412) 647-2240</td>
<td>1 (512) 647-7196</td>
<td><a href="mailto:HCPharmacy@upmc.edu">HCPharmacy@upmc.edu</a></td>
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### Distribution for Federal Accounts (Veterans Administration & Department of Defense)

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<td>McKesson Plasma &amp; Biologics</td>
<td>1 (877) 625-2566</td>
<td>1 (888) 752-7626</td>
<td><a href="http://www.connect.mckesson.com">www.connect.mckesson.com</a></td>
</tr>
<tr>
<td>Cardinal Health Specialty Pharmaceutical Distribution</td>
<td>1 (866) 677-4844</td>
<td>1 (888) 345-4916</td>
<td>specialtyonline.cardinalhealth.com</td>
</tr>
<tr>
<td>ASD Healthcare</td>
<td>1 (800) 746-6273</td>
<td>1 (800) 547-9413</td>
<td><a href="mailto:asd.customerservice@asdhealthcare.com">asd.customerservice@asdhealthcare.com</a></td>
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<tr>
<td>DMS Pharmaceutical Group, Inc.</td>
<td>1 (847) 518-1100</td>
<td>1 (847) 518-1105</td>
<td><a href="mailto:customerservice@dmspharma.com">customerservice@dmspharma.com</a></td>
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### Distribution for In-Patient Hospitals

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<td>McKesson Specialty Health</td>
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<td>1 (800) 547-9413</td>
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<td>1 (787) 999-1616</td>
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*This is a comprehensive list of GILOTRIF distributors as of April 3, 2014. This information is provided for the convenience of our customers and may change or be updated from time to time.

Please see Indication and Important Safety Information on reverse and accompanying full Prescribing Information, including Patient Information.
INDICATION AND LIMITATION OF USE
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.

Limitation of Use: Safety and efficacy of GILOTRIF have not been established in patients whose tumors have other EGFR mutations.

WARNINGS AND PRECAUTIONS

Diarrhea
- Diarrhea has resulted in dehydration with or without renal impairment; some of these cases were fatal. In the pivotal study, 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. 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. 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.

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. In the pivotal study, the overall incidence of cutaneous reactions consisting of rash, erythema, and acniform 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. For patients who develop prolonged Grade 2 cutaneous adverse reactions lasting more than 120 hours, 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.

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 the pivotal study, 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.

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 the pivotal study, 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. In patients who develop severe hepatic impairment while taking GILOTRIF, treatment should be discontinued.

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 the pivotal study, 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. 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. Contact lens use is also a risk factor for keratitis and ulceration.

Embryofetal Toxicity
- GILOTRIF is Pregnancy Category D. Based on its mechanism of action, GILOTRIF can cause fetal harm when administered to a pregnant woman. 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.

- 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.

Combination with Vinorelbine in HER2 Positive Metastatic Breast Cancer
- An early interim overall survival analysis of a randomized Phase 3 trial in HER2 positive metastatic breast cancer showed an increased mortality in patients receiving GILOTRIF in combination with vinorelbine compared to trastuzumab and vinorelbine. The combination of GILOTRIF and vinorelbine was also associated with a higher rate of adverse events (such as diarrhea, rash) and fatal events related to infections and cancer progression. GILOTRIF combined with vinorelbine should not be used in patients with HER2 positive metastatic breast cancer.

ADVERSE REACTIONS

Effect of P-glycoprotein (P-gp) Inhibitors and Inducers
- Concomitant taking of P-gp inhibitors (including but not limited to ritonavir, cyclosporine A, ketoconazole, licothromycin, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) with GILOTRIF can increase exposure to afatinib.

- 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.

USE IN SPECIFIC POPULATIONS

Nursing Mothers
- It is not known whether afatinib is present in human milk. 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.

Renal Impairment
- GILOTRIF has not been studied in patients with severely impaired renal function. Closely monitor patients with moderate (CrCl 30-59 mL/min) to severe (CrCl <30 mL/min) renal impairment and adjust GILOTRIF dose if not tolerated.

Hepatic Impairment
- GILOTRIF has not been studied in patients with severe (Child Pugh C) hepatic impairment. Closely monitor patients with severe hepatic impairment and adjust GILOTRIF dose if not tolerated.

抄写内容包括：

Embryofetal Toxicity
- GILOTRIF is Pregnancy Category D. Based on its mechanism of action, GILOTRIF can cause fetal harm when administered to a pregnant woman. 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.

- 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.

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USE IN SPECIFIC POPULATIONS

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- It is not known whether afatinib is present in human milk. 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.

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- GILOTRIF has not been studied in patients with severely impaired renal function. Closely monitor patients with moderate (CrCl 30-59 mL/min) to severe (CrCl <30 mL/min) renal impairment and adjust GILOTRIF dose if not tolerated.

Hepatic Impairment
- GILOTRIF has not been studied in patients with severe (Child Pugh C) hepatic impairment. Closely monitor patients with severe hepatic impairment and adjust GILOTRIF dose if not tolerated.

Please see accompanying full Prescribing Information, including Patient Information

Boehringer Ingelheim Pharmaceuticals, Inc.

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Copyright © 2014. Boehringer Ingelheim Pharmaceuticals, Inc.
GILOTRIF® (afatinib) tablets, for oral use
Initial U.S. Approval: 2013

RECENT MAJOR CHANGES

Warnings and Precautions

Combination with vinorelbine in HER2 positive metastatic breast cancer (5.7) 4/2014

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)

DOSE AND ADMINISTRATION

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

DOSE 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)
- Instruct patients to take GILOTRIF at least 1 hour before or 2 hours after a meal (2.2)

ADVERSE REACTIONS

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

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2.2 Recommended Dose
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3 DOSE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
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5.7 Combination with Vinorelbine in HER2 Positive Metastatic Breast Cancer
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7 DRUG INTERACTIONS

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/Drugs/InformationOnDrugs/ucm115168.htm

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)]

- 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)

For patients who require chronic therapy with a P-gp inducer, increase GILOTRIF daily dose 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)

8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Females and Males of Reproductive Potential

8.7 Renal Impairment

8.8 Hepatic Impairment

10 OVERDOSE

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12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

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

Permanently discontinue GILOTRIF for:

- 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 Inducers

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

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

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.

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

Revised: 04/2014
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)]
- Bulbous 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 (0.4%), and pneumonia (0.4%).

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/vacc (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%), I LD (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 as well as 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 dilatation; 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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>GILOTRIF n=229</th>
<th>Pemetrexed/Cisplatin n=111</th>
<th>All Grades (%)</th>
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<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Decreased appetite</td>
<td>29</td>
<td>4</td>
<td>55</td>
<td>4</td>
<td></td>
<td></td>
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<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>17</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>11</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>17</td>
<td>1</td>
<td>14</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 None of the adverse reactions in this table except stomatitis (one patient on GILOTRIF [0.4%]) were Grade 4 in severity.
2 Includes stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration
3 Includes group of rash prefered terms, acne, acne purulera, dermatitis acneform
4 Includes paronychia, nail infection, nail bed infection

5.7 Combination with Vinorelbine in HER2 Positive Metastatic Breast Cancer

An early interim overall survival analysis of a randomized Phase 3 trial in HER2 positive metastatic breast cancer showed an increased mortality in patients receiving GILOTRIF in combination with vinorelbine compared to trastuzumab and vinorelbine. The combination of GILOTRIF and vinorelbine was also associated with a higher rate of adverse events (such as diarrhea, rash) and fatal events related to infections and cancer progression. GILOTRIF combined with vinorelbine should not be used in patients with HER2 positive metastatic breast cancer.
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, saquinavir, neflertavir, 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 worth) 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 is 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 to the recommended human dose of 40 mg/day) 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 to the recommended human dose of 40 mg/day) 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 to the recommended human dose of 40 mg/day) 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 to the recommended human dose of 40 mg/day).

8.3 Nursing Mothers

It is not known whether afatinib is present in human milk. 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 to the recommended human dose of 40 mg/day) 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 to the recommended human dose of 40 mg/day) 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 to the recommended human dose of 40 mg/day).

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 old. Overall differences were observed between patients 65 years and older and younger patients. In Study 1, 39% of the 345 patients were 65 years or 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 (21)].

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. Close monitor patients with moderate (Clcr 30-59 mL/min) or severe (Clcr <30 mL/min) renal impairment and adjust GILOTRIF dose if 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)].
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,ο-∞) and 22% (Cmax) [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® (afatinib) tablets 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 FM03; 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 vivo 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

**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 determined by the IRC and stratified by EGFR mutation status and race.

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 mutation 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 L858O 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 3: Efficacy Results of Study 1**

<table>
<thead>
<tr>
<th>EGFR Mutation Category</th>
<th>HR (95% CI)</th>
<th>Median PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del19/L858R (Common)</td>
<td>0.47</td>
<td>13.6</td>
</tr>
<tr>
<td>Del19 (n=170)</td>
<td>0.28</td>
<td>13.7</td>
</tr>
<tr>
<td>L858R (n=138)</td>
<td>0.73</td>
<td>10.8</td>
</tr>
<tr>
<td>Other (Uncommon; n=37)</td>
<td>1.89</td>
<td>2.8</td>
</tr>
</tbody>
</table>

**Table 4: Objective Tumor Responses in Gilotrif®-Treated Patients Based on Investigator Assessment in the “Other” (Uncommon) EGFR Mutation Subgroup**

<table>
<thead>
<tr>
<th>EGFR Mutation</th>
<th>Number of Patients With Partial Response</th>
<th>Duration of Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>L858R and T790M</td>
<td>5</td>
<td>6.9 months</td>
</tr>
<tr>
<td>L858R and S768I</td>
<td>2</td>
<td>12.4 months</td>
</tr>
<tr>
<td>S768I</td>
<td>1</td>
<td>15.6 months</td>
</tr>
<tr>
<td>G719X</td>
<td>3</td>
<td>9.6 months</td>
</tr>
</tbody>
</table>

*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

**Table 5: Efficacy Results of Study 2**

<table>
<thead>
<tr>
<th>EGFR Mutations</th>
<th>Number of Gilotrif®-Treated Patients</th>
<th>Number of Patients With Partial Response</th>
<th>Duration of Response</th>
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CR=complete response; PR=partial response.

**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 mutation 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 L858O alone (n=3). There were 11 chemotherapy-treated patients in the “other” uncommon EGFR mutation subgroup; of these, four (36%) achieved a partial response.

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<td>3</td>
<td>9.6 months</td>
</tr>
</tbody>
</table>

*Stratified by EGFR mutation status and race.

CR=complete response; PR=partial response.

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: 0597-0141-30
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 12 hours or more after the last dose, skip the dose and 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® (afatinib) tablets.

• 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.