About Gilotrif®
(afatinib) tablets

Gilotrif® [pronounced JEE-loh-trif] (afatinib) tablets for oral use 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.

GILOTRIF is an oral, once-daily kinase inhibitor that is designed to bind to and irreversibly inhibit the following receptors: EGFR (ErbB1), HER2 (ErbB2) and ErbB4.

Please see the Important Safety Information starting below.

Metastatic NSCLC and Common EGFR Mutations

EGFR is a specific protein found on the surface of cells. In some people, genetic mutations involving EGFR lead to its constant activation, which is associated with uncontrolled cell division and the growth and development of metastatic NSCLC.

Among patients diagnosed with NSCLC (the most common form of lung cancer), it is estimated that between 10 and 15 percent of Caucasians and approximately 40 percent of Asians have EGFR mutations – which in 90 percent of cases are one of the two most common EGFR mutations (Del19 or L858R).

Supporting GILOTRIF Approval Companion Diagnostic

The approved NDA and aforementioned indication and usage for GILOTRIF is supported by the LUX-Lung 3 trial – one of the largest Phase III trials conducted to date in the first-line EGFR mutation-positive, locally advanced or metastatic NSCLC treatment setting.

To determine if a patient is eligible for GILOTRIF, physicians must conduct a test for genetic mutations – also known as biomarker testing – to determine if a common EGFR mutation is present. For this reason, BI collaborated with QIAGEN, a leading global provider of sample and assay technologies, on the development of a companion diagnostic for GILOTRIF. QIAGEN’s therascreen® EGFR RGQ PCR Kit was reviewed and approved by the FDA in parallel to GILOTRIF and will be used to identify patients who may be eligible for treatment.

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

IMPORTANT SAFETY INFORMATION

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

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IMPORTANT SAFETY INFORMATION (cont.)

• 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 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. 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.

**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.

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IMPORTANT SAFETY INFORMATION (cont.)

- 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
- In GILOTRIF-treated patients (n=229) the most common adverse reactions in the pivotal study (≥20% all grades & vs pemetrexed/cisplatin-treated patients (n=111) were diarrhea (96% vs 23%), rash/dermatitis acneiform (90% vs 11%), stomatitis (71% vs 15%), paronychia (58% vs 0%), dry skin (31% vs 2%), decreased appetite (29% vs 55%), pruritus (21% vs 1%).

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Important Safety Information (cont.)

- 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 included pulmonary toxicity/ILD-like adverse reactions (1.3%), sepsis (0.43%), and pneumonia (0.43%).

- 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).

Drugs 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.

- 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 (CLcr 30-59 mL/min) to severe (CLcr <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.

For full prescribing information, including patient information, please click here. You can also visit www.gilotrif.com or contact Boehringer Ingelheim’s Medical and Technical Information (MTI) Unit at 1-800-542-6257.

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