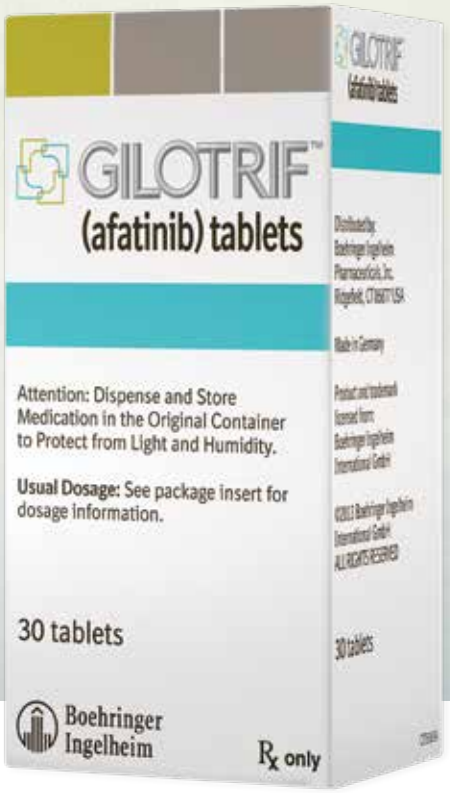
STRATEGIES AND INFORMATION TO

Help Your Patients Get the Benefits Associated With GILOTRIF and Continued Therapy



INDICATIONS AND USAGE

- **GILOTRIF is indicated for** the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test.

  Limitations of Use: Safety and efficacy of GILOTRIF have not been established in patients whose tumors have resistant EGFR mutations.
- **GILOTRIF is indicated for** the treatment of patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy.

Please see Important Safety Information starting on page 2, and accompanying full Prescribing Information, including Patient Information.

GILOTRIF® (afatinib) tablets

GILOTRIF: Nearly 3 years overall survival (OS) in patients with del19 mutations in LUX-Lung 3[1]

Median PFS in del19: 13.7 months with GILOTRIF vs 5.6 months with pemetrexed-cisplatin, HR, 0.28 (95% CI, 0.18–0.44) in a prespecified subanalysis of the primary endpoint[1,3]

*In a prespecified subgroup analysis of patients with del19 mutation for the secondary endpoint of OS.

LUX-Lung 3 Study Design

- A randomized (2:1), multicenter, open-label trial with EGFR M+ 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
  – Tumor samples from 264 patients (178 randomized to GILOTRIF and 86 patients rendomized to chemotherapy) were tested retrospectively by the companion diagnostic therascreen® EGFR RGQ PCR Kit
- GILOTRIF 40 mg orally once daily (n=230) vs IV pemetrexed (500 mg/m^2)-cisplatin (75 mg/m^2) once every 21 days for up to 6 cycles (n=115)
- Randomization was stratified according to EGFR mutation category (exon 19 deletion vs exon 21 L858R vs other) and race (Asian vs non-Asian)
- Primary endpoint was PFS, as assessed by an IRC; secondary endpoints included OS
- All efficacy analyses were performed in an intent-to-treat manner and included all randomized patients

CI=confidence interval; EGFR M+=epidermal growth factor receptor mutation-positive; HR=hazard ratio; IRC=independent review committee; IV=intravenous; NSCLC=non-small-cell lung cancer; OS=overall survival; PFS: progression-free survival

SELECTED IMPORTANT SAFETY INFORMATION FOR GILOTRIF® (afatinib) TABLETS

WARNINGS AND PRECAUTIONS

Diarrhea

- GILOTRIF can cause diarrhea which may be severe and can result in dehydration with or without renal impairment. In clinical studies, some of these cases were fatal.
- For patients who develop Grade 2 diarrhea lasting more than 48 hours or Grade 3 or greater diarrhea, withhold GILOTRIF until diarrhea resolves to Grade 1 or less, and then resume at a reduced dose.
- 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 until loose stools cease for 12 hours.

Please see Important Safety Information continued on following pages, and accompanying full Prescribing Information, including Patient Information.

GILOTRIF: An approved treatment option for patients with L858R (exon 21 substitution) mutations[1,2]

Median PFS in L858R: 10.8 months with GILOTRIF vs 8.1 months with pemetrexed-cisplatin, HR: 0.73 (95% CI, 0.46-1.17) in a prespecified subanalysis of the primary endpoint[2,3]

†In a prespecified subgroup analysis of patients with L858R mutations for the secondary endpoint of OS.

SELECTED IMPORTANT SAFETY INFORMATION FOR GILOTRIF® (afatinib) TABLETS

WARNINGS AND PRECAUTIONS

Bullous and Exfoliative Skin Disorders

- GILOTRIF can result in cutaneous reactions consisting of rash, erythema, and acneiform rash. In addition, palmar-plantar erythrodysesthesia syndrome was observed in clinical trials in patients taking GILOTRIF.
- Discontinue GILOTRIF in patients who develop life-threatening bullous, blistering, or exfoliating skin lesions. For patients who develop Grade 2 cutaneous adverse reactions lasting more than 7 days, intolerable Grade 2, or Grade 3 cutaneous reactions, withhold GILOTRIF. When the adverse reaction resolves to Grade 1 or less, resume GILOTRIF with appropriate dose reduction.

GILOTRIF: Established safety profile

Adverse reactions reported in LUX-Lung 3 in ≥10% of GILOTRIF-treated patients[2]

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

Other clinically important adverse reactions observed in patients treated with GILOTRIF include: decreased appetite (29%), nausea (25%), and vomiting (23%)[2]

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

SELECTED IMPORTANT SAFETY INFORMATION FOR GILOTRIF® (afatinib) TABLETS

WARNINGS AND PRECAUTIONS

Bullous and Exfoliative Skin Disorders (cont'd)

- Postmarketing cases of toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (SJS) have been reported in patients receiving GILOTRIF. Discontinue GILOTRIF if TEN or SJS is suspected.

Please see Important Safety Information continued on following pages, and accompanying full Prescribing Information, including Patient Information.

GILOTRIF: Serious adverse reactions and discontinuations

Serious adverse reactions reported in LUX-Lung 3[2]

- 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%)

Discontinuations in LUX-Lung 3[2]

- Discontinuation of therapy in GILOTRIF-treated patients for adverse reactions was 14%
- The most frequent adverse reactions that led to discontinuation in GILOTRIF-treated patients were diarrhea (1.3%), ILD (0.9%), and paronychia (0.9%)

Serious adverse reactions reported in LUX-Lung 8[2]

- Serious adverse reactions occurred in 44% of patients treated with GILOTRIF. The most frequent serious adverse reactions in patients treated with GILOTRIF were pneumonia (6.6%), diarrhea (4.6%), and dehydration and dyspnea (3.1% each). Fatal adverse reactions in GILOTRIF-treated patients included ILD (0.5%), pneumonia (0.3%), respiratory failure (0.3%), acute renal failure (0.3%), and general physical health deterioration (0.3%)

SqCC=squamous cell carcinoma.

SELECTED IMPORTANT SAFETY INFORMATION FOR GILOTRIF® (afatinib) TABLETS

WARNINGS AND PRECAUTIONS

Interstitial Lung Disease

- Interstitial Lung Disease (ILD) or ILD-like adverse reactions (e.g., lung infiltration, pneumonitis, acute respiratory distress syndrome, or alveolitis allergic) occurred in patients receiving GILOTRIF in clinical trials. In some cases, ILD was fatal. The incidence of ILD appeared to be higher in Asian patients as compared to white patients.
- Withhold GILOTRIF during evaluation of patients with suspected ILD, and discontinue GILOTRIF in patients with confirmed ILD.

IN ADVANCED SqCC OF THE LUNG PROGRESSING AFTER PLATINUM-BASED CHEMOTHERAPY

GILOTRIF: Significant improvement in PFS and OS vs erlotinib in LUX-Lung 8[2]

Median PFS and median OS in LUX-Lung 8[2,4]

51% (201/398) OF PATIENTS TREATED WITH GILOTRIF WERE ABLE TO ACHIEVE DISEASE CONTROL VS 40% WITH ERLOTINIB[4]

- Excluding patients with non-complete response and non-progressive disease, disease control with afatinib was 37%, vs 29% with erlotinib, in a post-hoc analysis[4]
- Median duration of objective response: 7.3 months (95% CI, 3.7-16.5) with GILOTRIF vs 3.7 months (95% CI, 2.6-10.2) with erlotinib[4]

GILOTRIF is the only oral, chemo-free option approved in metastatic squamous NSCLC regardless of mutation status[2,4]
No biomarker testing required[2,4]

LUX-Lung 8 Study Design[2,4]

- A head-to-head, phase 3, open-label, randomized trial of GILOTRIF 40 mg (n=398) vs erlotinib 150 mg (n=397) in patients with metastatic squamous NSCLC with disease progression following ≥4 cycles of platinum-based chemotherapy
- Primary endpoint was PFS as assessed by an IRC using RECIST v1.1
- Secondary endpoints included OS and objective response rates as assessed by an IRC

SELECTED IMPORTANT SAFETY INFORMATION FOR GILOTRIF® (afatinib) TABLETS

WARNINGS AND PRECAUTIONS

Hepatic Toxicity

- Hepatic toxicity as evidenced by liver function tests abnormalities has been observed in patients taking GILOTRIF. In 4257 patients who received GILOTRIF across clinical trials, 9.7% had liver test abnormalities, of which 0.2% were fatal.
- Obtain periodic liver testing in patients during treatment with GILOTRIF. Withhold GILOTRIF in patients who develop worsening of liver function. Discontinue treatment in patients who develop severe hepatic impairment while taking GILOTRIF.

Please see Important Safety Information continued on following pages, and accompanying full Prescribing Information, including Patient Information.

Adverse reactions[4]

- 44% of patients in each treatment arm experienced serious adverse reactions[4]

Adverse reactions reported in LUX-Lung 8 in ≥10% of GILOTRIF-treated patients[2]

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

[a]Includes stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration.

[b]Includes acne, dermatitis, acneiform dermatitis, eczema, erythema, exfoliative rash, folliculitis, rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin exfoliation, skin fissures, skin lesion, skin reaction, skin toxicity, skin ulcer.

[c]Includes paronychia, nail infection, nail bed infection.

Treatment-related discontinuation due to any adverse reactions was similar in both arms (20% vs 17% for GILOTRIF vs erlotinib)[4]

The most frequent adverse reactions that led to discontinuation in GILOTRIF-treated patients were diarrhea (4.1%) and rash/acne (2.6%)[2]

SELECTED IMPORTANT SAFETY INFORMATION FOR GILOTRIF® (afatinib) TABLETS

WARNINGS AND PRECAUTIONS

Gastrointestinal Perforation

- Gastrointestinal (GI) perforation, including fatal cases, has occurred with GILOTRIF. GI perforation has been reported in 0.2% of patients treated with GILOTRIF among 3213 patients across 17 randomized controlled clinical trials.
- Patients receiving concomitant corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), or anti-angiogenic agents, or patients with increasing age or who have an underlying history of GI ulceration, underlying diverticular disease, or bowel metastases may be at an increased risk of perforation.
- Permanently discontinue GILOTRIF in patients who develop GI perforation.

Tolerability-guided dose modification can be an important strategy to help manage adverse reactions[2,3]

Initiate

- Initiate therapy at the recommended 40 mg dose*

Evaluate

- Evaluate patients for adverse reactions within 2 weeks and periodically thereafter

Pause

- Pause treatment for ≥ grade 3 adverse reactions†
- Or ≥ grade 2
  - diarrhea (prolonged)‡
  - cutaneous reactions (prolonged or intolerable)§
  - renal impairment

Resume

- Resume treatment at 10 mg less per day when adverse reaction fully resolves, returns to baseline, or improves to grade 1

*In patients with pre-existing severe renal impairment, the recommended dose of vGILOTRIF is 30 mg orally once daily.
†National Cancer Institute Common Terminology Criteria for Adverse Events, v4.03.
‡Grade ≥2 diarrhea persisting ≥48 hours while taking antidiarrheal medication.
§Grade 2 cutaneous reactions >7 days.

Permanently discontinue GILOTRIF for[2]:

Life-threatening bullous, blistering, or exfoliative skin lesions; confirmed ILD; severe drug-induced hepatic impairment; gastrointestinal perforation; persistent ulcerative keratitis; symptomatic left ventricular dysfunction; and severe or intolerable adverse reaction occurring at a dose of 20 mg per day.

SELECTED IMPORTANT SAFETY INFORMATION FOR GILOTRIF® (afatinib) TABLETS

WARNINGS AND PRECAUTIONS

Keratitis

- Keratitis has been reported in patients taking GILOTRIF.
- Withhold GILOTRIF during evaluation of patients with suspected keratitis. If diagnosis of ulcerative keratitis is confirmed, interrupt or discontinue GILOTRIF. 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.

Please see Important Safety Information continued on following pages, and accompanying full Prescribing Information, including Patient Information.

GILOTRIF Dose Exchange™ facilitates transition to a new dose†

For patients who experienced an adverse reaction requiring a dose reduction

- Dose modifications may help with adverse reactions. GILOTRIF Dose Exchange™ is designed to make dose adjustments seamless for your patients
- Eligible patients receive a new dose without an additional co-pay (free of charge)
- Patients receive new dose of GILOTRIF prior to returning their previous, unused tablets
- Call 1-877-814-3915 to learn more

†GILOTRIF Dose Exchange™ covers up to 2 dose modifications for patients serviced through Accredo® or GILOTRIF Dispensing Network who have 9 or more tablets to exchange.

Recommended dose[2]

- The recommended dose is 40 mg orally once daily
- In patients with pre-existing severe renal impairment, the recommended dose of GILOTRIF is 30 mg orally once daily‡

‡Estimated glomerular filtration rate [eGFR] 15 to 29 mL/min/1.73 m^2.

How to take[2]

- 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

Treatment duration[2]

- Treatment should be continued until disease progression or until no longer tolerated by the patient

Multiple strengths[2]

- Multiple tablet strengths are available for dose adjustment

GILOTRIF 40-mg tablet
Not actual size.

GILOTRIF 30-mg tablet
Not actual size.

GILOTRIF 20-mg tablet
Not actual size.

SELECTED IMPORTANT SAFETY INFORMATION FOR GILOTRIF® (afatinib) TABLETS

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity

- GILOTRIF can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.
- Advise females of reproductive potential to use effective contraception during treatment, and for at least 2 weeks after the last dose of GILOTRIF. Advise female patients to contact their healthcare provider with a known or suspected pregnancy.

GILOTRIF: Tolerability-guided dose adjustment reduced the frequency and severity of treatment-related adverse reactions[5]

LUX-Lung 3: Over half of patients reduced dose[2]

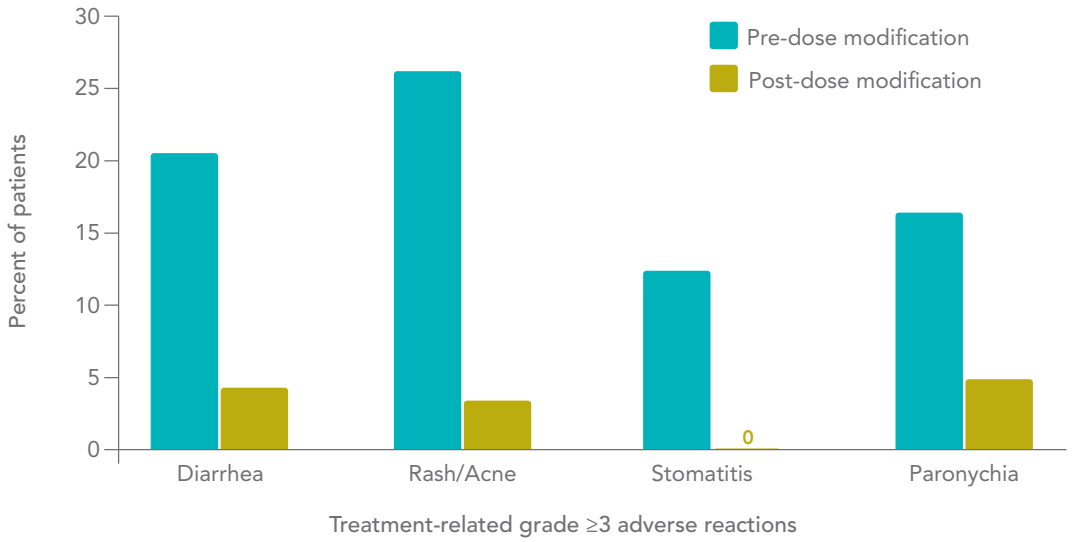
43% maintained 40 mg starting dose

38% reduced to 30 mg

19% reduced to 20 mg

Among patients that dose reduced in LUX-Lung 3 (n=89) based on grade ≥3 ARs[5]

Grade ≥3 adverse reactions* with dose modifications[5†]



*Selected based on the 4 most common treatment-related adverse reactions pre- and post-dose reduction in LUX-Lung 3.
†Post hoc analysis included all of afatinib-treated patients in LUX-Lung 3.

- The most frequent adverse reactions that led to dose reduction in the patients treated with GILOTRIF were diarrhea (20%), rash/acne (19%), stomatitis (10%), and paronychia (14%)[2]

SELECTED IMPORTANT SAFETY INFORMATION FOR GILOTRIF® (afatinib) TABLETS

ADVERSE REACTIONS

Adverse Reactions observed in clinical trials were as follows:

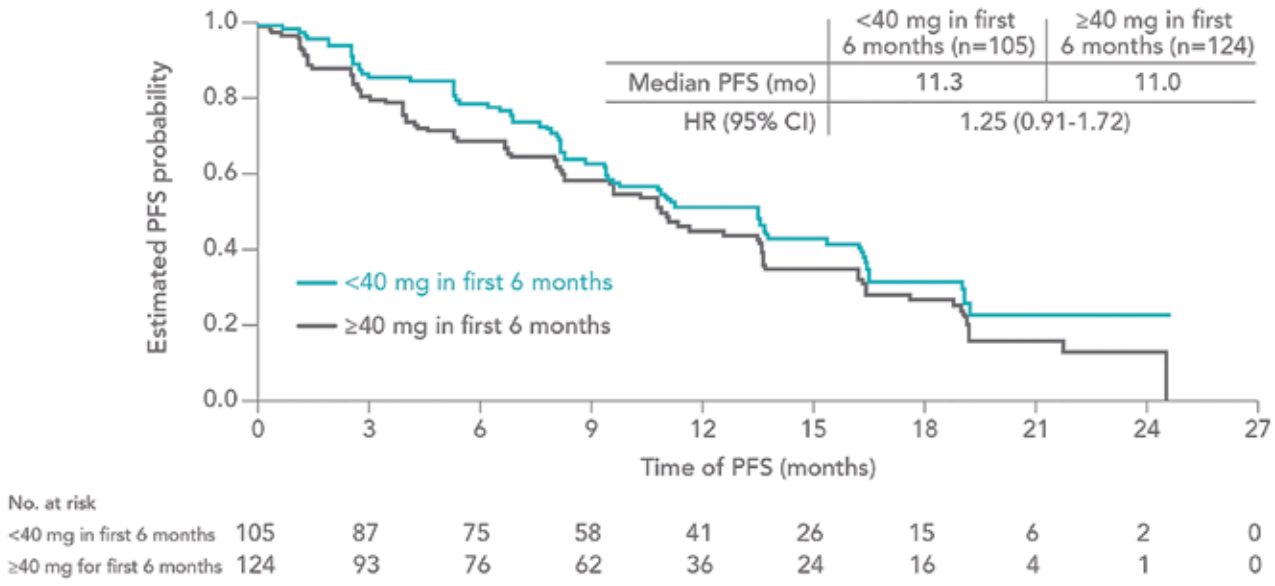
First-line treatment of EGFR mutation-positive, metastatic NSCLC

- In GILOTRIF-treated patients (n=229) the most common adverse reactions (≥20% all grades & vs pemetrexed/cisplatin-treated patients (n=111)) were diarrhea (96% vs 23%), rash/acneiform dermatitis (90% vs 11%), stomatitis (71% vs 15%), paronychia (58% vs 0%), dry skin (31% vs 2%) and pruritus (21% vs 1%). Other clinically important adverse reactions observed in patients treated with GILOTRIF include: decreased appetite (29%), nausea (25%), and vomiting (23%).

Please see Important Safety Information continued on following pages, and accompanying full Prescribing Information, including Patient Information.

In a post hoc analysis of LUX-Lung 3, PFS results were consistent among patients who required dose reductions within the first 6 months and those who remained on GILOTRIF 40 mg[5‡]

PFS in patients with or without dose reductions within the first 6 months[5‡]



‡Data from intention-to-treat population, which includes both patients with common and uncommon EGFR mutations.

SELECTED IMPORTANT SAFETY INFORMATION FOR GILOTRIF® (afatinib) TABLETS

ADVERSE REACTIONS

Adverse Reactions observed in clinical trials were as follows: (cont'd)

First-line treatment of EGFR mutation-positive, metastatic NSCLC (cont'd)

- 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%) experienced ventricular dysfunction (defined as diastolic dysfunction, left ventricular dysfunction, or ventricular dilation; all < Grade 3) compared to chemotherapy-treated patients (0.9%).

Previously Treated, Metastatic Squamous NSCLC

- In GILOTRIF-treated patients (n=392) the most common adverse reactions (≥20% all grades & vs erlotinib-treated patients (n=395)) were diarrhea (75% vs 41%), rash/acneiform dermatitis (70% vs 70%), stomatitis (30% vs 11%), decreased appetite (25% vs 26%), and nausea (21% vs 16%).
- Serious adverse reactions were reported in 44% of patients treated with GILOTRIF. The most frequent serious adverse reactions reported in patients treated with GILOTRIF were pneumonia (6.6%), diarrhea (4.6%), and dehydration and dyspnea (3.1% each). Fatal adverse reactions in GILOTRIF-treated patients included ILD (0.5%), pneumonia (0.3%), respiratory failure (0.3%), acute renal failure (0.3%), and general physical health deterioration (0.3%).

Diarrhea management

In GILOTRIF-treated patients from LUX-Lung 3[2]:

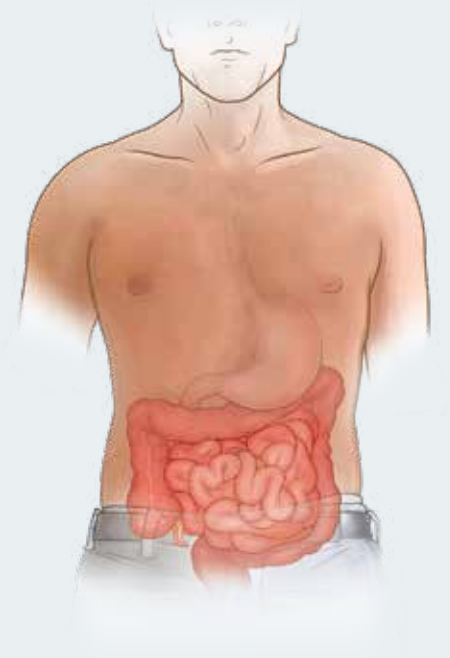
96% of patients reported diarrhea

83% of patients who had diarrhea had their first episode occur within the first 14 days of treatment

1.3% of patients discontinued treatment due to diarrhea

15% of patients reported grade 3 events within the first 6 weeks

20% of patients had their dose of GILOTRIF reduced due to diarrhea



Patient counseling tips

Recommend[6,7]

Drink enough fluids to avoid dehydration. Take an antidiarrheal agent at the first sign of symptoms, continuing until loose bowel movements cease for 12 hours. Avoid laxatives and stool softeners, as well as milk products, caffeine, and alcohol. Eat small, frequent meals consisting of easy-to-digest foods such as bananas and rice.

Advise[2]

Diarrhea occurs in nearly all patients who take GILOTRIF. Diarrhea may result in dehydration and renal impairment if left untreated. Call your office right away if diarrhea develops.

Please see Important Safety Information continued on following pages, and accompanying full Prescribing Information, including Patient Information.

CTCAE grading and trial protocol interventions[8,9]

Grade 1	Grade 2	Grade 3	Grade 4
<4 stools	**4-6 stools**	**≥7 stools**	**Life-threatening**
Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4-6 stools per day over baseline; not interfering with daily activities; IV fluids indicated <24 hrs; moderate increase in ostomy output compared to baseline	Increase of ≥7 stools per day over baseline; incontinence; interfering with daily activities; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline	Life-threatening consequences (eg, hemodynamic collapse)
Maintain dose	**Prolonged: Pause**	**Pause**	**Pause**
Continue same dose of GILOTRIF. Stop laxatives and advise patient to drink 8-10 glasses of water or clear fluids per day. Prescribe 4 mg loperamide taken immediately, followed by 2 mg after each loose stool (max. 16 mg/day) until bowel movements cease for 12 hours	Continue same dose of GILOTRIF unless grade 2 diarrhea continues for ≥48 hours, in which case GILOTRIF must be paused until reduced to ≤ grade 1; follow with dose reduction. See grade 1; continue loperamide; assess for dehydration and electrolyte imbalance; consider IV fluids and electrolyte replacement	Pause GILOTRIF until recovered to ≤ grade 1 and follow with dose reduction. In addition to grade 2 interventions, an infectious process should be ruled out with stool cultures; aggressive IV fluid replacement ≥24 hours; hospitalization to monitor progress; consider prophylactic antibiotics if patient is also neutropenic	**See Grade 3**

Please see full dose modification guidance for GILOTRIF on page 8.

CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous.

Rash/Acne management

In GILOTRIF-treated patients from LUX-Lung 3[2]:

90% of patients reported cutaneous reactions consisting of rash, erythema, and acneiform rash

16% of patients reported grade 3 events

64% of GILOTRIF-treated patients experienced rash/acne within the first 14 days of treatment

19% of patients reduced their dose of GILOTRIF due to rash/acne

There were no reports of discontinuation of GILOTRIF due to rash/acne[2]

Patient counseling tips

Recommend

- Minimize sun exposure by using protective clothing and sunscreen and use sunscreen (SPF ≥15) when outside, applying generously every 2 hours or more frequently if sweating or swimming[6,10]
- Use a mild soap in the shower, and avoid soaps with strong scents. Shower with lukewarm water and avoid long, hot showers, and apply an emollient to dry areas within 15 minutes of showering or bathing[6]
- Use hypoallergenic products that do not have perfumes or preservatives. Contact your office as soon as rash develops[10]

SPF=sun protection factor.

SELECTED IMPORTANT SAFETY INFORMATION FOR GILOTRIF® (afatinib) TABLETS

DRUG INTERACTIONS

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

- Concomitant use 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 use 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.

Please see Important Safety Information continued on following pages, and accompanying full Prescribing Information, including Patient Information.

CTCAE grading and trial protocol interventions[8,9]

Rash (desquamation)

Grade 1	Grade 2	Grade 3	Grade 4
Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering >30% BSA with or without mild symptoms	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated
Maintain dose	**Pause**	**Pause**	**Permanently Discont.**
Topical steroids[a] or tacrolimus ointment alternative. Consider topical antibiotics[b] twice daily. Recommend cream for isolated scattered lesions, and lotion for multiple scattered areas	Topical steroid treatment as for grade 1 oral antibiotic (for 6 weeks) eg, doxycycline 100 mg b.i.d., minocycline hydrochloride 100 mg b.i.d., or, if available, oxytetracycline 500 mg b.i.d. Stop topical antibiotic if being used	Topical and systemic treatment as for grade 2. If infection suspected (yellow crusts, purulent discharge, painful skin/nares), switch oral antibiotic to broad spectrum/gram negative coverage and consider skin swab for bacterial culture	Permanently discontinue GILOTRIF for life-threatening bullous, blistering, or exfoliative skin lesions

Rash (acne/acneiform): **Grade 1**—intervention not indicated; **grade 2**—intervention indicated; **grade 3**—associated with pain, disfigurement, ulceration, or desquamation; **grade 4**—n/a.[8]

Please see full dose modification guidance for GILOTRIF on page 8.

[a]eg, moderate/low strength: triamcinolone acetonide 0.025%, desonide 0.05%, alclometasone 0.05%, fluticasone propionate 0.05%, hydrocortisone acetate 1%.

[b]eg, clindamycin 1%-2%, or topical erythromycin 1%-2%, cream of metronidazole 1%, or topical nadifloxacin 1%.

BSA=body surface area.

Paronychia management

In GILOTRIF-treated patients from LUX-Lung 3[2]:

58% reported experiencing paronychia

11% reported grade 3 paronychia

14% experienced dose reduction due to paronychia

0.9% discontinued treatment due to paronychia

Patient counseling tips

Recommend

Keep affected areas dry. Avoid nail trauma such as overly aggressive manicures/pedicures, biting the nails, and contact with irritating substances.[11]

Advise

Patients exposed to moist environments such as bartenders, dishwashers, and swimmers should take extra precautions to ensure that their nails are dry and clean.[11]

SELECTED IMPORTANT SAFETY INFORMATION FOR GILOTRIF® (afatinib) TABLETS

USE IN SPECIFIC POPULATIONS

Lactation

- Because of the potential for serious adverse reactions in breastfed infants from GILOTRIF, advise women not to breastfeed during treatment with GILOTRIF and for 2 weeks after the final dose.

Females and Males of Reproductive Potential

- GILOTRIF may reduce fertility in females and males of reproductive potential. It is not known if the effects on fertility are reversible.

Please see Important Safety Information continued on following pages, and accompanying full Prescribing Information, including Patient Information.

CTCAE grading and trial protocol interventions[8,12]

Grade 1	Grade 2	Grade 3
Nail fold edema or erythema; disruption of the cuticle	Localized intervention indicated; oral intervention indicated (eg, antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self-care ADL
Maintain dose	**Prolonged: Pause**	**Pause**
Topical antibiotics/antiseptics[a], vinegar soaks[b], and topical ultrapotent steroids	Topical antibiotics[a], vinegar soaks[b], silver nitrate application weekly, and topical ultrapotent steroids	Topical antibiotics[a], vinegar soaks[b], silver nitrate application weekly/consider nail avulsion and systemic antibiotics

Please see full dose modification guidance for GILOTRIF on page 8.

Fissures

The following interventions were included in clinical study protocols for GILOTRIF[9]:

Mild (grade 1)—asymptomatic: Petroleum jelly (Vaseline®), or Aquaphor® for 30 minutes under plastic occlusion nightly, followed by application of hydrocolloid dressing; antiseptic baths; or topical applications.
Moderate (grade 2)—symptomatic, not interfering with ADL: See grade 1 and consider oral antibiotics.
Severe (grade 3)—symptomatic, interfering with ADL: See grade 2.

[a]Examples of topical antibiotics/antiseptics: clindamycin 1%, erythromycin 1%, tetracycline 1%, or chloramphenicol 1%; iodine ointment.

[b]Vinegar soaks consist of soaking fingers or toes in a solution of white vinegar in water 1:1 for 15 minutes every day. Systemic antibiotics include tetracyclines and antimicrobials (the potent P-gp inhibitor erythromycin should be avoided).

ADL=activities of daily living.

Stomatitis management

In GILOTRIF-treated patients from LUX-Lung 3[2]:

71% reported stomatitis

9% reported a grade 3 event

0.4% (1 patient) experienced grade 4 stomatitis

10% of GILOTRIF-treated patients had their dose reduced due to stomatitis

Patient counseling tips

Recommend

- Mouthwash containing lidocaine or benzocaine can provide short-term relief. Use systemic analgesics as needed.[16] Practice good mouth care, such as using a soft toothbrush to gently brush the teeth[14]
- Rinse with salt/baking soda/water after every meal and at bedtime, and use lip balm or petroleum jelly for dry lips[14]
- Eat foods cold or at room temperature, as hot and warm food can irritate a tender mouth, and try to eat soft, soothing, and moist food, such as mashed potatoes or scrambled eggs[15]
- Avoid acidic or irritating juices and foods, spicy or salty foods, and rough or coarse foods like raw vegetables, granola, or toast. Drink plenty of water, using a straw[15]

SELECTED IMPORTANT SAFETY INFORMATION FOR GILOTRIF® (afatinib) TABLETS

USE IN SPECIFIC POPULATIONS

Renal Impairment

- Patients with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 mL/min/1.73 m^2) have a higher exposure to afatinib than patients with normal renal function. Administer GILOTRIF at a starting dose of 30 mg once daily in patients with severe renal impairment. GILOTRIF has not been studied in patients with eGFR <15 mL/min/1.73 m^2 or who are on dialysis.

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.

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Please see Important Safety Information on following pages, and accompanying full Prescribing Information, including Patient Information.

CTCAE grading and trial protocol interventions[8,9]

Grade 1	Grade 2	Grade 3	Grade 4
Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences
Maintain dose	**Prolonged: Pause**	**Pause**	**Pause**
Oral rinses with agents such as nonalcoholic mouthwash, normal saline, diluted salt and baking soda solution	Addition of topical analgesic mouth treatments, topical corticosteroids, antiviral therapy if herpetic infection confirmed, antifungal therapy preferably topical on a case by case basis	Same as for grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated	Same as for grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated

Please see full dose modification guidance for GILOTRIF on page 8.

NCI CTCAE Grading Scale[8,17]

Grading criteria are based on versions 3.0 and 4.03 of the CTCAE

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4-6 stools per day over baseline; not interfering with daily activities; IV fluids indicated <24 hrs; moderate increase in ostomy output compared to baseline	Increase of ≥7 stools per day over baseline; incontinence; interfering with daily activities; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline	Life-threatening consequences (eg, hemodynamic collapse)
Rash (desquamation)	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering >30% BSA with or without mild symptoms	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated
Rash (acne/acneiform)	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	—
Dry skin	Covering <10% BSA and no associated erythema or pruritus	Covering 10%-30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self-care ADL	—

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Pruritus (a disorder characterized by an intense itching sensation)	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self-care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	—
Mucositis/ stomatitis (a disorder characterized by inflammation of the oral mucosa)	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences
Paronychia (a disorder characterized by an infectious process involving the soft tissues around the nail)	Nail fold edema or erythema; disruption of the cuticle	Localized intervention indicated; oral intervention indicated (eg, antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self-care ADL	—

NCI=National Cancer Institute.

IMPORTANT SAFETY INFORMATION FOR GILOTRIF® (afatinib) TABLETS

WARNINGS AND PRECAUTIONS

Diarrhea

- GILOTRIF can cause diarrhea which may be severe and can result in dehydration with or without renal impairment. In clinical studies, some of these cases were fatal.
- For patients who develop Grade 2 diarrhea lasting more than 48 hours or Grade 3 or greater diarrhea, withhold GILOTRIF until diarrhea resolves to Grade 1 or less, and then resume at a reduced dose.
- 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 until loose stools cease for 12 hours.

Bullous and Exfoliative Skin Disorders

- GILOTRIF can result in cutaneous reactions consisting of rash, erythema, and acneiform rash. In addition, palmar-plantar erythrodysesthesia syndrome was observed in clinical trials in patients taking GILOTRIF.
- Discontinue GILOTRIF in patients who develop life-threatening bullous, blistering, or exfoliating skin lesions. For patients who develop Grade 2 cutaneous adverse reactions lasting more than 7 days, intolerable Grade 2, or Grade 3 cutaneous reactions, withhold GILOTRIF. When the adverse reaction resolves to Grade 1 or less, resume GILOTRIF with appropriate dose reduction.
- Postmarketing cases of toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (SJS) have been reported in patients receiving GILOTRIF. Discontinue GILOTRIF if TEN or SJS is suspected.

Interstitial Lung Disease

- Interstitial Lung Disease (ILD) or ILD-like adverse reactions (e.g., lung infiltration, pneumonitis, acute respiratory distress syndrome, or alveolitis allergic) occurred in patients receiving GILOTRIF in clinical trials. In some cases, ILD was fatal. The incidence of ILD appeared to be higher in Asian patients as compared to white patients.
- Withhold GILOTRIF during evaluation of patients with suspected ILD, and discontinue GILOTRIF in patients with confirmed ILD.

Hepatic Toxicity

- Hepatic toxicity as evidenced by liver function tests abnormalities has been observed in patients taking GILOTRIF. In 4257 patients who received GILOTRIF across clinical trials, 9.7% had liver test abnormalities, of which 0.2% were fatal.
- Obtain periodic liver testing in patients during treatment with GILOTRIF. Withhold GILOTRIF in patients who develop worsening of liver function. Discontinue treatment in patients who develop severe hepatic impairment while taking GILOTRIF.

Gastrointestinal Perforation

- Gastrointestinal (GI) perforation, including fatal cases, has occurred with GILOTRIF. GI perforation has been reported in 0.2% of patients treated with GILOTRIF among 3213 patients across 17 randomized controlled clinical trials.
- Patients receiving concomitant corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), or anti-angiogenic agents, or patients with increasing age or who have an underlying history of GI ulceration, underlying diverticular disease, or bowel metastases may be at an increased risk of perforation.
- Permanently discontinue GILOTRIF in patients who develop GI perforation.

Keratitis

- Keratitis has been reported in patients taking GILOTRIF.
- Withhold GILOTRIF during evaluation of patients with suspected keratitis. If diagnosis of ulcerative keratitis is confirmed, interrupt or discontinue GILOTRIF. 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.

Embryo-Fetal Toxicity

- GILOTRIF can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.
- Advise females of reproductive potential to use effective contraception during treatment, and for at least 2 weeks after the last dose of GILOTRIF. Advise female patients to contact their healthcare provider with a known or suspected pregnancy.

ADVERSE REACTIONS

Adverse Reactions observed in clinical trials were as follows:

First-line treatment of EGFR mutation-positive, metastatic NSCLC

- In GILOTRIF-treated patients (n=229) the most common adverse reactions (≥20% all grades & vs pemetrexed/cisplatin-treated patients (n=111)) were diarrhea (96% vs 23%), rash/acneiform dermatitis (90% vs 11%), stomatitis (71% vs 15%), paronychia (58% vs 0%), dry skin (31% vs 2%) and pruritus (21% vs 1%). Other clinically important adverse reactions observed in patients treated with GILOTRIF include: decreased appetite (29%), nausea (25%), and vomiting (23%).
- 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%) experienced ventricular dysfunction (defined as diastolic dysfunction, left ventricular dysfunction, or ventricular dilation; all < Grade 3) compared to chemotherapy-treated patients (0.9%).

Previously Treated, Metastatic Squamous NSCLC

- In GILOTRIF-treated patients (n=392) the most common adverse reactions (≥20% all grades & vs erlotinib-treated patients (n=395)) were diarrhea (75% vs 41%), rash/acneiform dermatitis (70% vs 70%), stomatitis (30% vs 11%), decreased appetite (25% vs 26%), and nausea (21% vs 16%).
- Serious adverse reactions were reported in 44% of patients treated with GILOTRIF. The most frequent s erious adverse reactions reported in patients treated with GILOTRIF were pneumonia (6.6%), diarrhea (4.6%), and dehydration and dyspnea (3.1% each). Fatal adverse reactions in GILOTRIF-treated patients included ILD (0.5%), pneumonia (0.3%), respiratory failure (0.3%), acute renal failure (0.3%), and general physical health deterioration (0.3%).

DRUG INTERACTIONS

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

- Concomitant use 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 use 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

Lactation

- Because of the potential for serious adverse reactions in breastfed infants from GILOTRIF, advise women not to breastfeed during treatment with GILOTRIF and for 2 weeks after the final dose.

Females and Males of Reproductive Potential

- GILOTRIF may reduce fertility in females and males of reproductive potential. It is not known if the effects on fertility are reversible.

Renal Impairment

- Patients with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 mL/min/1.73 m^2) have a higher exposure to afatinib than patients with normal renal function. Administer GILOTRIF at a starting dose of 30 mg once daily in patients with severe renal impairment. GILOTRIF has not been studied in patients with eGFR <15 mL/min/1.73 m^2 or who are on dialysis.

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.

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Please see accompanying full Prescribing Information, including Patient Information.

GILOTRIF: The growing body of evidence

- Broadest 1st-line indication of any TKI approved for EGFR M+ mNSCLC
- Proven efficacy in 1st-line OS and PFS in Del 19, and PFS in L858R[2,16]
- Significantly improved OS and PFS vs erlotinib in patients with advanced squamous cell carcinoma of the lung whose disease has progressed after treatment with platinum-based chemotherapy[2]
- Established safety profile based on data from >17,000 patients treated[5,9*]
  - **>4,000 patients treated in clinical studies and >13,000 treated since approval**
- GILOTRIF dose modification
  - **Dose modification reduced the frequency and severity of adverse reactions[16]**
  - **GILOTRIF Dose Exchange™ facilitates transition to a new dose**

INDICATIONS AND USAGE

- **GILOTRIF is indicated for** the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test.

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

- **GILOTRIF is indicated for** the treatment of patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy.

Please see Important Safety Information starting on page 2, and accompanying full Prescribing Information, including Patient Information.

References: 1. Yang JC-H, Wu Y-L, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol.* 2015;16(2):141-151. **2.** Gilotrif® (afatinib) tablets Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. **3.** Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol.* 2013;31(27):3327-3334. **4.** Soria J-C, Felip E, Cobo M, et al. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. *Lancet Oncol.* 2015;16:897-907. **5.** Yang JC, Sequist LV, Zhou C, et al. Effect of dose adjustment on the safety and efficacy of afatinib for EGFR mutation-positive lung adenocarcinoma: post hoc analyses of the randomized LUX-Lung 3 and 6 trials [published online September 6, 2016]. *Ann Oncol.* 2016. doi: 10.1093/annonc/mdw322. **6.** Hirsh V. Managing treatment-related adverse events associated with EGFR tyrosine kinase inhibitors in advanced non-small-cell lung cancer. *Curr Oncol.* 2011;18(3):126-138. **7.** Cancernetwork.com. Diarrhea in cancer patients. http://www.cancernetwork.com/oncology-nursing/diarrhea-cancer-patients. Accessed June 29, 2020. **8.** Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. **9.** Data on file. Boehringer Ingelheim. Trial protocol. **10.** Cancer.net. Skin reactions to targeted therapy and immunotherapy. http://www.cancer.net/navigating-cancer-care/side-effects/skin-reactions-targeted-therapy-and-immunotherapy. Accessed June 29, 2020. **11.** Rockwell PG. Acute and chronic paronychia. *Am Fam Physician.* 2001;63(6):1113-1116. **12.** Lacouture ME, Schadendorf D, Chu CY, et al. Dermatologic adverse events associated with afatinib: an oral ErbB family blocker. *Expert Rev Anticancer Ther.* 2013;13(6):721-728. **13.** Bensinger W, Schubert M, Ang KK, et al. NCCN Task Force Report: prevention and management of mucositis in cancer care. *J Natl Compr Canc Netw.* 2008;6(suppl 1):S1-S21. **14.** National Cancer Institute. Managing chemotherapy side effects. https://www.cancer.gov/publications/patient-education/mouth-and-throat.pdf. Accessed June 29, 2020. **15.** National Cancer Institute. Nutrition in cancer care. Mucositis/stomatitis. http://www.cancer.gov/about-cancer/treatment/side-effects/appetite-loss/nutrition-hp-pdq#link/_138_toc. Accessed June 29, 2020. **16.** National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: non-small cell lung cancer, version 5.2020. http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed June 29, 2020.

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