Afatinib: Drug information

(For additional information see "Afatinib: Patient drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

Brand Names: US

Gilotrif

Brand Names: Canada

Giotrif

Pharmacologic Category

Antineoplastic Agent, Epidermal Growth Factor Receptor (EGFR) Inhibitor; Antineoplastic Agent, Tyrosine Kinase Inhibitor

Dosing: Adult

Non-small cell lung cancer (NSCLC), metastatic, with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations: Oral: 40 mg once daily until disease progression or unacceptable toxicity

NSCLC, metastatic squamous: Oral: 40 mg once daily until disease progression or unacceptable toxicity

Missed doses: Do not take a missed dose within 12 hours of next dose

Dosage adjustment for concomitant therapy:

P-gp inhibitors: If concomitant therapy is not tolerated, reduce afatinib daily dose by 10 mg. Upon discontinuation of the P-gp inhibitor, resume previous dose as tolerated.

P-gp inducers: Increase afatinib daily dose by 10 mg as tolerated if on chronic concomitant therapy with a P-gp inducer. Resume previous dose 2 to 3 days after discontinuation of P-gp inducer.

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

Note: The manufacturer recommends using the Modification of Diet in Renal Disease (MDRD) formula to estimate the glomerular filtration rate (eGFR).

Preexisting impairment:

eGFR >30 mL/minute/1.73 m^2: No dosage adjustment is necessary.

eGFR 15 to 29 mL/minute/1.73 m^2: Reduce dose to 30 mg once daily.

eGFR <15 mL/minute/1.73 m^2 and hemodialysis: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

Renal toxicity during treatment: If ≥ grade 2 renal toxicity occurs, withhold therapy. Upon improvement

to baseline or ≤ grade 1, resume therapy at 10 mg per day less than previous dose.

Dosing: Hepatic Impairment

Preexisting mild to moderate impairment (Child-Pugh class A or B): No dosage adjustment is necessary.

Preexisting severe impairment (Child-Pugh class C): There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); closely monitor and adjust dose if necessary.

Hepatotoxicity during treatment: Withhold therapy for ≥ grade 3 hepatic dysfunction. Upon improvement to baseline or ≤ grade 1, resume therapy at 10 mg per day less than previous dose. Permanently discontinue for severe afatinib-induced hepatic impairment.

Dosing: Adjustment for Toxicity

Note: Permanently discontinue for intolerability or severe reaction occurring at a dose of 20 mg daily.

Cardiovascular: Permanently discontinue for symptomatic left ventricular dysfunction.

Dermatologic: Withhold therapy for prolonged (>7 days) or intolerable grade 2 or higher cutaneous reactions. Upon improvement to baseline or ≤ grade 1, resume therapy at 10 mg per day less than previous dose. Discontinue permanently for life-threatening bullous, blistering, or exfoliative skin lesions, as well as for suspected toxic epidermal necrolysis (TEN) or Stevens Johnson syndrome (SJS).

Gastrointestinal:

Diarrhea: Grade 2 or higher diarrhea that persists for ≥2 consecutive days despite antidiarrheal therapy: Interrupt therapy until resolution to ≤ grade 1, then resume at 10 mg per day less than previous dose.

Nausea/vomiting: For intolerable grade 2 or persistent (≥7 days) nausea/vomiting despite antiemetic therapy, the following recommendations have been made: Interrupt therapy for up to 14 days until resolution to ≤ grade 1, then resume at 10 mg per day less than previous dose; if symptoms do not resolve within 14 days, discontinue permanently (Giotrif Canadian product labeling 2016).

Ocular: Interrupt therapy for suspected keratitis; consider discontinuation if diagnosis of ulcerative keratitis is confirmed. Permanently discontinue for persistent ulcerative keratitis.

Pulmonary: Interrupt therapy for suspected interstitial lung disease (ILD); permanently discontinue if diagnosis is confirmed.

Other toxicity: Grade 3 or higher adverse reactions: Withhold therapy for ≥ grade 3 adverse reactions. Upon improvement to baseline or ≤ grade 1, resume therapy at 10 mg per day less than previous dose.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, Oral:

Gilotrif: 20 mg

Gilotrif: 30 mg, 40 mg [contains fd&c blue #2 (indigotine)]

Generic Equivalent Available (US) No

Dosage Forms: Canada Information with regard to form, strength, and availability of products uniquely available in Canada but currently not available in the US. Refer also to Dosage forms.

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, Oral:

Giotrif: 20 mg, 30 mg, 40 mg

Administration Administer orally at least 1 hour before or 2 hours after a meal. Do not take a missed dose within 12 hours of the next dose.

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage. NIOSH recommends single gloving for administration of intact tablets or capsules (NIOSH 2016).

Use

Non-small cell lung cancer, metastatic, EGFR mutation-positive: First-line treatment of metastatic non-small cell lung cancer (NSCLC) in patients whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an approved test.

Limitations of use: Safety and efficacy have not been established in patients whose tumors express EGFR mutations other than exon 19 deletion or exon 21 (L858R) substitution.

Non-small cell lung cancer, metastatic squamous: Treatment of previously treated metastatic squamous cell NSCLC which has progressed following platinum-based chemotherapy.

Medication Safety Issues

Sound-alike/look-alike issues:

Afatinib may be confused with Afinitor, alectinib, axitinib, ceritinib, crizotinib, erlotinib, gefitinib

High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Adverse Reactions

>10%:

Dermatologic: Acneiform eruption (≤70% to 90%; grade 3: ≤16%), skin rash (≤70% to 90%; grade 3: ≤16%), paronychia (11% to 58%), xeroderma (31%), pruritus (10% to 21%), cheilitis (12%)

Endocrine & metabolic: Decreased serum potassium (11% to 30%), weight loss (17%), hypokalemia (11%)

Gastrointestinal: Diarrhea (75% to 96%; grade 3: 15%; grades 3/4: 11% to 16%), stomatitis (30% to 71%), decreased appetite (25% to 29%), nausea (21% to 25%), vomiting (13% to 23%)

Genitourinary: Cystitis (13%)

Hematologic & oncologic: Abnormal lymphocytes (decreased: 38%; grades 3/4: 9%), decreased white blood cell count (12%; grades 3/4: 1%)

Hepatic: Increased serum ALT (10% to 54%; grades 3/4: 1% to 2%), increased serum alkaline phosphatase (34% to 51%; grades 3/4: 2% to 3%), increased serum AST (7% to 46%; grades 3/4: 1% to 3%), abnormal hepatic function tests (6% to 18%; grades 3/4: ≤4%), increased serum bilirubin (3% to 16%; grades 3/4: ≤1%)

Ophthalmic: Conjunctivitis (11%)

Renal: Decreased creatinine clearance (49%; grades 3/4: 2%)

Respiratory: Epistaxis (17%), rhinorrhea (11%)

Miscellaneous: Fever (12%)

1% to 10%:

Central nervous system: Fatigue (<2%)

Dermatologic: Palmar-plantar erythrodysesthesia (2% to 7%)

Ophthalmic: Keratitis (≤2%; grade 3: <1%)

Renal: Renal insufficiency (6%; grade 3: >1%)

Respiratory: Interstitial pulmonary disease (2%; grades 3/4: ≤1%), dyspnea (<2%)

Frequency not defined:

Endocrine & metabolic: Dehydration

Infection: Sepsis

Renal: Acute renal failure

Respiratory: Pneumonia

Miscellaneous: Physical health deterioration

<1%, postmarketing, and/or case reports: Pancreatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis

Contraindications

US labeling: There are no contraindications listed in the manufacturer's labeling.

Canadian labeling: Hypersensitivity to afatinib or any component of the formulation.

Warnings/Precautions

Concerns related to adverse effects:

• Cardiovascular toxicity: Decreases from baseline in left ventricular ejection fraction (LVEF) were noted in some patients receiving afatinib. Patients with abnormal LVEF or a significant cardiac history were excluded from clinical trials; use with caution in patients with cardiac risk factors and/or decreased LVEF.

• Dermatologic toxicity: Cutaneous reactions (eg, acneiform rash, erythema, and rash) are common; grade 3 reactions (characterized by bullous, blistering, and exfoliating lesions) and palmar-plantar erythrodysesthesia syndrome were also seen in clinical trials. Cases of skin reactions consistent with Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported; SJS and TEN result from a mechanism which is distinct and separate from the bullous skin toxicity typically observed with EGFR inhibitor therapy. Dermatologic toxicity may require therapy interruption and dosage reduction; discontinue if life-threatening bullous, blistering, or exfoliating lesions occur or for suspected SJS or TEN. Patients should be cautioned to avoid sun exposure and/or utilize adequate sun protection.

• Gastrointestinal toxicity: In clinical trials, diarrhea (including grade 3 and 4 events) and stomatitis frequently occurred in patients treated with afatinib; diarrhea was observed in the majority of patients and typically appeared within the first 6 weeks of therapy. Dehydration and renal impairment may occur as a consequence of diarrhea; monitor closely. Patients may require antidiarrheal therapy (eg, loperamide); initiate at the onset of diarrhea and continue until free of loose bowel movements for 12 hours. May necessitate therapy interruption and dosage reduction.

• Hepatotoxicity: Hepatic function test abnormalities (some fatal) were observed in clinical trials. Monitor liver function tests periodically; may require therapy interruption and dosage reduction. Discontinue if severe hepatic impairment occurs during therapy.

• Ocular toxicity: Keratitis (including rare grade 3 events) was reported rarely in clinical trials; monitor for signs/symptoms of keratitis (eg, acute or worsening eye inflammation, blurred vision, eye pain, lacrimation, light sensitivity, red eye). Interrupt therapy in patients with suspected keratitis and consider discontinuation if diagnosis of ulcerative keratitis is confirmed (permanently discontinue for persistent ulcerative keratitis). Use with caution in patients with a history of keratitis, severe dry eye, ulcerative keratitis, or who wear contact lens (risk factor for keratitis and ulceration).

• Paronychia: Paronychia requiring dose reduction and discontinuation of therapy has been observed.

• Pulmonary toxicity: Interstitial lung disease (ILD) or ILD-like reactions occurred in a small percentage of patients treated with afatinib (some fatal). ILD incidence appeared to be higher in Asian as compared to non-Asian patients. Monitor closely for signs/symptoms of ILD (eg, acute respiratory distress syndrome, allergic alveolitis, lung infiltration, pneumonitis). Interrupt therapy for suspected ILD; discontinue therapy with confirmed diagnosis.

Disease-related concerns:

• Hepatic impairment: Use in severe hepatic impairment (Child-Pugh class C) has not been studied; closely monitor patients with severe impairment, may require dosage adjustments if not tolerated.

• Renal impairment: Dosage reduction is recommended in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 mL/minute/1.73 m^2).

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

Dosage forms specific issues:

• Lactose: Formulation may contain lactose.

Other warnings/precautions:

• Appropriate use: Safety and efficacy have not been established in patients with non-small cell lung cancer whose tumors express EGFR mutations other than exon 19 deletion or exon 21 (L858R) substitution. Increased mortality has been observed in a clinical trial evaluating afatinib in combination with vinorelbine for HER2-positive metastatic breast cancer (not an approved use). This combination was also associated with a higher incidence of adverse events (eg, diarrhea, rash), as well as fatalities due to infection and cancer progression. Afatinib should not be used in combination with vinorelbine for the treatment of HER2-positive metastatic breast cancer.

Metabolism/Transport Effects

Substrate of BCRP, P-glycoprotein; **Inhibits** BCRP

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Aminolevulinic Acid: Photosensitizing Agents may enhance the photosensitizing effect of Aminolevulinic Acid. *Risk C: Monitor therapy*

CarBAMazepine: May decrease the serum concentration of Afatinib. Management: Per US labeling: if requiring chronic use of carbamazepine, increase afatinib dose by 10 mg as tolerated; reduce to original afatinib dose 2-3 days after stopping carbamazepine. Per Canadian labeling: avoid combination if possible. *Risk D: Consider therapy modification*

Lumacaftor: May decrease the serum concentration of P-glycoprotein/ABCB1 Substrates. Lumacaftor may increase the serum concentration of P-glycoprotein/ABCB1 Substrates. *Risk C: Monitor therapy*

Nelfinavir: May increase the serum concentration of Afatinib. Management: Per US labeling: reduce afatinib by 10 mg if not tolerated. Per Canadian labeling: avoid combination if possible; if used, administer nelfinavir simultaneously with or after the dose of afatinib. *Risk D: Consider therapy modification*

P-glycoprotein/ABCB1 Inducers: May decrease the serum concentration of Afatinib. Management: Per US labeling: if requiring chronic use of P-gp inducers, increase afatinib dose by 10mg as tolerated; reduce to original afatinib dose 2-3 days after stopping P-gp inducers. Per Canadian labeling: avoid

combination if possible. *Risk D: Consider therapy modification*

P-glycoprotein/ABCB1 Inhibitors: May increase the serum concentration of Afatinib. Management: Per US labeling: reduce afatinib by 10mg if not tolerated. Per Canadian labeling: avoid combination if possible; if used, administer the P-gp inhibitor simultaneously with or after the dose of afatinib. *Risk D: Consider therapy modification*

PHENobarbital: May decrease the serum concentration of Afatinib. Management: Per US labeling: if requiring chronic use of phenobarbital, increase afatinib dose by 10 mg as tolerated; reduce to original afatinib dose 2-3 days after stopping phenobarbital. Per Canadian labeling: avoid combination if possible. *Risk D: Consider therapy modification*

Porfimer: Photosensitizing Agents may enhance the photosensitizing effect of Porfimer. *Risk C: Monitor therapy*

Primidone: May decrease the serum concentration of Afatinib. Management: Per US labeling: if requiring chronic use of primidone, increase afatinib dose by 10 mg as tolerated; reduce to original afatinib dose 2-3 days after stopping primidonel. Per Canadian labeling: avoid combination if possible. *Risk D: Consider therapy modification*

Saquinavir: May increase the serum concentration of Afatinib. Management: Per US labeling: reduce afatinib by 10 mg if not tolerated. Per Canadian labeling: avoid combination if possible; if used, administer saquinavir simultaneously with or after the dose of afatinib. *Risk D: Consider therapy modification*

Tacrolimus (Systemic): May increase the serum concentration of Afatinib. Management: Per US labeling: reduce afatinib by 10 mg if not tolerated. Per Canadian labeling: avoid combination if possible; if used, administer tacrolimus simultaneously with or after the dose of afatinib. *Risk D: Consider therapy modification*

Verteporfin: Photosensitizing Agents may enhance the photosensitizing effect of Verteporfin. *Risk C: Monitor therapy*

Food Interactions Administration with a high-fat meal decreases C_{max} by 50% and AUC by 39% as compared to the fasted state. Management: Take at least 1 hour before or 2 hours after a meal.

Pregnancy Implications Based on animal reproduction studies and on the mechanism of action, afatinib may cause fetal harm if used during pregnancy. Women of reproductive potential should use highly-effective contraception during therapy and for at least 2 weeks after treatment has been discontinued.

Breast-Feeding Considerations It is not known if afatinib is excreted into breast milk. Due to the potential for serious adverse reactions in the breast-feeding infant, the manufacturer recommends against breast-feeding during therapy and for at least 2 weeks after treatment has been discontinued.

Monitoring Parameters EGFR mutation status; liver and renal function (periodically); monitor for skin toxicity, diarrhea, signs/symptoms of dehydration; monitor for signs/symptoms of interstitial lung disease (eg, acute respiratory distress syndrome, allergic alveolitis, lung infiltration, pneumonitis) and keratitis (eg, acute or worsening eye inflammation, blurred vision, eye pain, lacrimation, light sensitivity, red eye). Consider left ventricular ejection fraction assessment prior to and during therapy in patients with cardiac risk factors or conditions that may impair left ventricular function.

Mechanism of Action Highly selective blocker of the ErbB family, including EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4); covalently and irreversibly binds to the intracellular tyrosine kinase domain, resulting in tumor growth inhibition and tumor regression. Inhibits autophosphorylation and proliferation (in vitro) in cell lines expressing both wild-type EGFR and selected EGFR mutations.

Pharmacodynamics/Kinetics

Absorption: Decreased with high-fat meals

Protein binding: ~95%

Metabolism: Covalently adducted to proteins and nucleophilic small molecules (minimal enzymatic metabolism) (Wind, 2013)

Bioavailability: Tablets: 92% (as compared to an oral solution)

Half-life elimination: 37 hours

Time to peak: 2 to 5 hours

Excretion: Feces (85%); urine (4%); primarily as unchanged drug

Pricing: US

Tablets (Gilotrif Oral)

20 mg (30): $9060.85

30 mg (30): $9060.85

40 mg (30): $9060.85

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names Giotrif (AR, AT, AU, BE, CH, CR, CU, CZ, DE, DK, DO, EC, EE, ES, FR, GB, GT, HK, HN, HR, HU, ID, IL, IS, JP, KR, LB, LT, LU, LV, MT, MY, NI, NL, NO, PA, PE, PH, PL, PT, QA, RO, SA, SE, SG, SI, SK, SV, TH)

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