DRUG NAME: Afatinib

SYNONYM(S): afatinib dimaleate[1], BIBW2992[2]

COMMON TRADE NAME(S): GIOTRIF®, GILOTRIF® (USA)

CLASSIFICATION: miscellaneous

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Afatinib is a second-generation tyrosine kinase inhibitor.[1] It binds to the kinase domains of EGFR, HER2 and HER4, irreversibly inhibiting tyrosine kinase autophosphorylation, and results in reduction of tumour growth and tumour regression.[3,4] Afatinib has activity against tumours that overexpress wild-type EGFR or HER2, and those having EGFR mutations (i.e., exon 19 deletion or exon 21 substitution). Afatinib may delay or prevent secondary resistance to EGFR tyrosine kinase inhibitors through its complete blockade of the signaling pathway.[1]

PHARMACOKINETICS:

Oral Absorption	bioavailability[3] 92%; time to peak 2-5 h; absorption reduced by presence of food (AUC reduced by 39%, C_{max} reduced by 50% after a high-fat meal; AUC reduced by 26% if taken within 1 hr before food or 3 hours after)	
Distribution	distributed in blood, plasma, and tissues	
	cross blood brain barrier?	yes; accumulation noted after repeat dosing
	volume of distribution	2770 L
	plasma protein binding	95%
Metabolism	minimal hepatic metabolism[2]	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	primarily as unchanged drug[3]	
	urine	4%
	feces	85%
	terminal half life	37 h
	clearance	900 mL/min

Adapted from standard reference[4] unless specified otherwise.

USES:

Primary uses:

*Lung cancer, non-small cell

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Caution:

- ***decreased left ventricular ejection fraction*** (LVEF) is reported; consider cardiac monitoring (including baseline LVEF) for patients with cardiac risk factors or conditions that may affect left ventricular function[4]

- ***diarrhea***, resulting in dehydration and hypokalemia, is reported; use with caution in patients who have gastrointestinal disorders with diarrhea as a major symptom (e.g., Crohn's disease, malabsorption)[4]
- ***gastrointestinal perforation*** is reported; known risk factors include history of gastrointestinal ulceration or diverticular disease, bowel metastases, and concomitant therapy with other drugs associated with GI perforation[5]

Special populations:
- ***Patients >65 years*** have reported more grade 3 adverse events, especially diarrhea.[4]
- ***Patients with underlying renal impairment*** may experience higher exposure to afatinib (increased C_{max} and AUC at steady state with reduced creatinine clearance), resulting in a higher risk of developing adverse effects typical of EGFR inhibitors, such as diarrhea, rash, and stomatitis.[4]
- ***Asian patients*** have a higher incidence of interstitial lung disease compared with non-Asians.[1]

Carcinogenicity: no information found

Mutagenicity: Mutagenic in Ames test. Afatinib is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[4]

Fertility: In animal studies, overall fertility was not affected, however an increase in the incidence of low or no sperm count was reported.[4] Reduced numbers of corpora lutea and increased post-implantation loss has also been reported.[6]

Pregnancy: FDA Pregnancy Category D.[1] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
No human studies have been conducted but fetal harm is expected based on the mechanism of action. In animal studies, abortions, skeletal alterations, reduced fetal weights, and visceral and dermal variations have been reported. Animal pre- and postnatal development studies have shown lower birth weights; although developmental landmarks, sexual maturation, and performance with behavioral assessments were not affected. Women of childbearing potential should use contraception continually during treatment and for 2 weeks after discontinuation of therapy.[4]

Breastfeeding is not recommended due to the potential secretion into breast milk. In animal studies, afatinib has been excreted in breast milk.[4]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[7]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia/hemoglobin decreased (1-3%)
	leucopenia (2%)
	lymphopenia (<1%)
	neutropenia (<1%)
cardiac	mitral valve incompetence (<1%)
	ventricular dysfunction (2%)
eye	conjunctivitis (8-11%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	keratitis (1-2%; severe <1%)[3,4]; see paragraph following **Side Effects** table
	vision disorders, including blepharitis, blurred vision, cataracts, increased lacrimation, dry eyes (1-5%)
gastrointestinal	*emetogenic potential:* low[8]
	abdominal distension or pain (2-3%)
	cheilitis (12%)
	constipation (3-13%)
	diarrhea (96%, severe 15%); see paragraph following **Side Effects** table
	dry mouth (4%)
	dyspepsia (4%)
	dysphagia (1%)
	gastroesophageal reflux disease (2%)
	gastrointestinal perforation (<1%); see paragraph following **Side Effects** table
	gingival bleeding (1%)
	nausea (18-25%, severe 1%)[4,9]
	pancreatitis, acute (<1%)
	proctalgia (1%)
	stomatitis (71%, severe 1-9%)[3,4]
	vomiting (5-23%, severe 4%)[3,4]
general disorders and administration site conditions	asthenia (4%)
	fatigue (18%, severe 1-2%)[3,9]
	peripheral edema (2-3%)
	pyrexia (5-12%)
hepatobiliary	***hepatic dysfunction***, including hepatic failure (1-2%); discontinue treatment if severe hepatic impairment develops
infections and infestations	cellulitis (1%)
	cystitis (4-13%, severe 1%)
	herpes zoster (1%)
	nasopharyngitis (14%)
	paronychia (58%, severe 11%); see paragraph following **Side Effects** table
	pneumonia (<1%)[3]
	rhinitis (2%)
	sepsis (<1%)
	upper respiratory tract infection (1-11%)
investigations	alkaline phosphatase increased (2-6%, severe 4%)
	ALT increased (7-11%, severe 2-3%)
	AST increased (5-8%, severe 2%)[4,6]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	amylase increased (<1%)
	bilirubin increased (1%, severe 2%)
	creatine phosphokinase increase (<1%)
	left ventricular ejection fraction decreased (6-25%); see paragraph following **Side Effects** table
	weight decreased (17%, severe 1%)
metabolism and nutrition	decrease appetite (21-29%, severe 3-4%)[4,9]
	dehydration (2%)
	hypocalcemia (<1%)
	hypokalemia (6-11%, severe 2-4%)
	hyponatremia (<1%)
musculoskeletal and connective tissue	arthralgia (1%)
	back pain (2-14%)
	muscle spasm (3%)
	musculoskeletal chest pain (1%)
	myalgia (2%)
nervous system	dizziness (4-11%)
	dysgeusia (7%)
	headache (5-14%)
	hypoesthesia (2%)
psychiatric	insomnia (5-15%)
renal and urinary	proteinuria (1%)
	renal impairment/failure (4-6%); may require dose reduction and/or interruption[3]
respiratory, thoracic and mediastinal	cough (3-15%)
	dyspnea (2%)
	epistaxis (13-17%)[4,9]
	hemoptysis (1%)
	interstitial lung disease (1%); permanently discontinue treatment
	nasal dryness (3%)
	oropharyngeal pain (2%)
	pneumonitis (>1%)[3]
	pulmonary embolism (<1%)
	rhinorrhea (10-11%)
skin and subcutaneous tissue; see paragraph following **Side Effects** table	alopecia (10-13%)
	dry skin (31%)
	hyperkeratosis (<1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hypertrichosis (3%)
	palmar-plantar erythrodysesthesia (7%)
	pruritus (21%)
	rash/dermatitis acneiform (35-90%, severe 3-16%)[4,6]
	skin hyperpigmentation (1%)
	Stevens-Johnson syndrome[5] (<1%); see paragraph following **Side Effects** table
	toxic epidermal necrolysis[5] (<1%); see paragraph following **Side Effects** table
vascular	hypertension (2%)

Adapted from standard reference[4] unless specified otherwise.

Diarrhea has been reported in 96% of patients receiving afatinib. Onset of diarrhea usually occurs within the first 2 weeks of treatment, with grade 3 diarrhea developing most frequently within the first 6 weeks. Close monitoring and early intervention is essential in preventing the development of more severe diarrhea which can result in dehydration, renal impairment and severe electrolyte imbalance. Rare cases of fatalities have been reported. Patients with severe diarrhea may require dose interruption and reduction, or discontinuation of therapy. Recommendations for management of diarrhea as follows[4]:

- Adequate hydration and anti-diarrheal agents (e.g., loperamide) should be initiated at the first sign of diarrhea; anti-diarrheal agents should be readily available at home.
    - First sign of any diarrhea: loperamide 4 mg immediately, followed by 2 mg with every loose bowel movement, up to a maximum of 20 mg loperamide daily; continue until 12 hours after the last loose bowel movement.
    - Grade 2 or 3 diarrhea: loperamide as above plus adequate hydration (1.5 L/m^2/day plus equivalent of actual fluid loss) and electrolyte replacement.
    - In addition, for grade 3 diarrhea or grade 2 diarrhea lasting 48 hours or longer despite adequate anti-diarrheal therapy: interrupt afatinib treatment until Grade 1 or less and resume at a reduced dose.
- Avoid foods that may aggravate diarrhea or lactose-containing products if patients are lactose-intolerant.
- Discontinue afatinib for diarrhea which does not resolve to Grade 1 or less within 14 days despite anti-diarrheal therapy and interruption of treatment.

Gastrointestinal perforation has been rarely reported with afatinib. However, approximately one-third of the reported cases have been fatal. The majority of patients have had other known risk factors including history of gastrointestinal ulceration or underlying diverticular disease, bowel metastases at the site of the perforation, or concomitant medications such as anti-angiogenic agents, corticosteroids, NSAIDs, etc., but in some cases, the patients have had no known predisposing risk factors. Permanently discontinue afatinib following gastrointestinal perforation.[5]

Decreased ***left ventricular ejection fraction*** (LVEF) has been reported with drugs that block HER2 activity. Up to 25% of patients on afatinib have experienced a 10-20% decrease in LVEF from baseline; a smaller percentage (6%) of patients had a LVEF decrease of greater than 20%. Consider cardiac consultation and treatment interruption/discontinuation in patients who develop cardiac signs/symptoms during treatment.[4]

Paronychia has been reported in 58% of patients and may require dose reduction or discontinuation of treatment. Preventative measures and good skin care may help to reduce the frequency and severity of paronychia[4]:

- avoid trauma to nails or fingertips;
- avoid harsh chemicals such as soaps, detergents and nail products
- keep hands clean and dry.

Topical antibiotics/antiseptics and/or steroids may be helpful for management of mild cases. For management of moderate or severe cases, topical or systemic antibiotics, steroids, and silver nitrate applications may be used.[4]

Skin-related adverse events include rash, dry skin, pruritus, and dermatitis acneiform. Rash generally manifests as a mild to moderate erythematous and acneiform rash and may occur or worsen in areas exposed to sun. Bullous, blistering, and exfoliative skin conditions have also been reported, as well as rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. Counsel patients to avoid sun exposure and wear sun protection. Early intervention may prevent the development of prolonged or severe reactions. Referral to a dermatologist may be required. Management may include topical or systemic steroids, anti-infectives, or antihistamines and may require that afatinib treatment be interrupted, dose reduced, or discontinued. If patients develop prolonged or severe skin reactions, afatinib should be permanently discontinued.[1,4,5]

A variety of ***visual disturbances*** has been reported, and may require an ophthalmology referral. Symptoms include acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye.[4] If keratitis is suspected, interrupt treatment. If a diagnosis of keratitis is confirmed, consider risk/benefit of treatment before continuing afatinib. Permanently discontinue treatment for persistent ulcerative keratitis.[1] Use with caution in patients with a history of keratitis, with or without ulceration, severe dry eyes, or those who wear contact lenses (a risk factor for keratitis and ulceration).[4]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
ritonavir[4]	• ritonavir given 1 hour prior to afatinib: afatinib AUC and C_{max} increased by 48% and 39% respectively • exposure was not significantly increased when ritonavir was administered either with or 6 hours after afatinib	inhibition of P-glycoprotein by ritonavir	administer simultaneously with or after afatinib; monitor for afatinib adverse effects
rifampin[4]	decreased afatinib AUC by 34% and C_{max} by 22%	induction of P-glycoprotein by rifampin	avoid concurrent treatment if possible

Afatinib is a substrate of P-glycoprotein (P-gp) and inhibitor of P-gp and Breast Cancer Resistance Protein (BCRP). Concurrent therapy with P-gp inducers may decrease afatinib exposure. Concurrent use with P-gp substrates may increase the exposure of the substrates. Concurrent therapy with strong P-gp inhibitors, given prior to afatinib, may lead to increased afatinib exposure; monitor for afatinib adverse effects. If concurrent therapy with P-gp inhibitors is required, give simultaneously with or after afatinib.[4]

SUPPLY AND STORAGE:

Oral: Boehringer Ingelheim (Canada) Ltd. supplies afatinib as 20 mg, 30 mg and 40 mg film-coated tablets. Store at room temperature. Keep in original packaging. Protect from moisture and light. Tablets contain lactose.[4]

Additional information: Tablets are provided in unit dose blister cards and packaged in laminated aluminum pouches with a desiccant. Tablets should be stored in the blister card inside the aluminum pouch until immediately prior to use. Tablets are stable at room temperature for 14 days once the aluminum package has been opened.[10,11]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

Oral[2,4,12]:	Cycle Length: ***40 mg*** (range 20-50 mg) ***PO once daily.*** Administer on an empty stomach (one hour before or three hours after food).
Concurrent radiation:	no information found
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"
Dosage in renal failure[5]:	• mild impairment (CrCl 60-90 mL/min): no adjustment required • moderate impairment (CrCl 30-59 mL/min): no adjustment required; monitor for adverse reactions • severe impairment o CrCl 15-29 mL/min: reduce starting dose to 30 mg PO once daily o CrCl <15 mL/min: avoid use Afatinib exposure is increased with decreased renal function (due to a reduced expression of P-glycoprotein in renal impairment).[13]
Dosage in hepatic failure[4]*:*	• mild to moderate impairment (Child-Pugh A or B): no adjustment required • severe impairment (Child-Pugh C): no information found
Dosage in dialysis[5]*:*	avoid use

***Children*:** no information found

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