Drug Monograph

A - Drug Name

AFAtinib

COMMON TRADE NAME(S): Giotrif®

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B - Mechanism of Action and Pharmacokinetics

Afatinib is an irreversible inhibitor of the ErbB family of tyrosine kinases, including epidermal growth factor receptor (EGFR), HER2 and HER4. It also inhibits transphosphorylation of HER3. EGFR inhibition plays a role in downregulating ErbB signaling, decreasing tumor cell proliferation and vascularization.

Absorption	Afatinib shows non-linear PK, with exposure increasing slightly more than proportional between 20 mg to 50 mg doses.	
	Peak plasma levels	2-5 hours
	Time to reach steady state	8 days, with 2.8x accumulation in exposure at steady state
	Effects with food	Administration following a high-fat meal decreased afatinib exposure by 50%. When food was consumed 3 hrs before or 1 hr after the dose, exposure decreased on average by 26%.
	Bioavailability	Unknown

Distribution	Afatinib is equally distributed into most tissues and covalently binds to albumin and hemoglobin. It accumulates in the retina and skin.	
	PPB	95%
	Cross blood brain barrier?	Low with single oral dosing, but accumulation occurs with repeat dosing.
Metabolism	Afatinib undergoes negligible enzymatic metabolism. Metabolized through Michael addition reactions resulting in adduct formation to proteins or small nucleophilic molecules.	
	Main enzymes involved	P-gp, BCRP
	Inactive metabolites	Yes
Elimination	Mainly excreted as parent drug	
	Half-life	37 hours (terminal, steady state)
	Feces	85%
	Urine	4%

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C - Indications and Status

Health Canada Approvals:

- Non-small cell lung cancer (NSCLC)

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

Extravasation Potential: Not applicable

The following table lists adverse effects that occurred in ≥ 10% of patients treated with afatinib in a pivotal phase III trial comparing afatinib to pemetrexed/cisplatin in patients with EGFR mutation positive metastatic adenocarcinoma of the lung. It also includes severe, life-threatening and post-marketing adverse effects from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Cardiotoxicity (<1%) (6% LVEF decrease of >20%)	E D
	Hypertension (2%)	E
	Venous thromboembolism (<1%)	E
Dermatological	Alopecia (13%)	D
	Dry skin (31%)	E
	Hand-foot syndrome (7%) (1% severe)	E
	Paronychia (58%) (11% severe)	E
	Rash, pruritus (71%) (severe 14%)	E
	Stevens-Johnson syndrome (rare)	E
	Toxic epidermal necrolysis (rare)	E
Gastrointestinal	Anorexia, weight loss (29%)	E
	Constipation (13%)	E
	Diarrhea (96%) (severe 15%)	E
	Dyspepsia (4%)	E
	GI perforation (<1%)	E
	Mucositis (71%) (severe 9%)	E
	Nausea, vomiting (25%)	E
Hematological	Myelosuppression (2%)	E
Hepatobiliary	↑ LFTs (11%) (may be severe)	E
	Pancreatitis (<1%)	E
Infection	Infection (14%) (including herpes zoster, rarely sepsis)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (11%) (hypokalemia)	E
Musculoskeletal	Musculoskeletal pain (14%)	E

Nervous System	Dizziness (11%)	E
	Dysgeusia (7%)	E
	Headache (14%)	E
	Insomnia (15%)	E
Ophthalmic	Cataract (1%) (or blurred vision)	E D
	Conjunctivitis (11%)	E
	Keratitis (2%)	E
Renal	Proteinuria (1%)	E
	Renal failure (4%)	E
Respiratory	Cough (15%)	E
	Epistaxis (17%)	E
	Other (11%) - Rhinorrhea	E
	Pneumonitis (1%) (may be severe)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for Afatinib include diarrhea, mucositis, rash, pruritus, paronychia, dry skin, anorexia, weight loss, nausea, vomiting, epistaxis, cough and insomnia.

Decreases in left-ventricular ejection fraction (LVEF) were observed in the afatinib arm of the pivotal trial, including decrease of > 20% from baseline or lower than the institution's lower limit of normal.

Severe **diarrhea** resulting in dehydration, hypokalemia, renal insufficiency and/or death has been reported. Diarrhea appears within the first 2 weeks of treatment, while severe cases occurred within the first 6 weeks of treatment. Patients should be adequately educated on early management and should have a sufficient supply of loperamide. Patients should avoid lactose-containing products or foods that aggravate diarrhea. Ensure hydration and electrolyte replacement is maintained if diarrhea occurs.

Gastrointestinal perforation, including fatal cases, has been rarely reported with afatinib. Patients receiving concomitant medications such as corticosteroids, NSAIDs, or anti-angiogenic agents may be at increased risk. Older patients or those with an underlying history of gastrointestinal ulceration, diverticular disease, or bowel metastases may also be at increased risk of perforation.

Keratitis has been reported with afatinib. Patients with acute or worsening ocular symptoms (e.g. eye inflammation, lacrimation, light sensitivity, blurred vision, or eye pain) should be referred promptly to an ophthalmologist. Patients should avoid the use of contact lenses during treatment, given an increased risk of keratitis.

Rash generally manifests itself as a mild to moderate erythematous and acneiform rash that may worsen with sun exposure. Patients should protect themselves from the sun. Stevens-Johnson syndrome and toxic epidermal necrolysis have also been reported rarely.

Paronychia is a common side effect. Patients should avoid trauma to nails, finger tips, and chemicals such as soaps, detergents and nail products. Topical antibiotics/antiseptics and/or steroids may be used to treat mild paronychia. For moderate to severe cases, topical or systemic antibiotics and/or steroids as well as periodic silver nitrate application may be beneficial.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

In patients with adenocarcinoma of the lung, EGFR mutation-positive status must be confirmed by a validated test before treatment.

- Safety and efficacy have not been established in patients with EGFR mutations other than exon 19-deletions (DEL19) and the exon 21 L858R point mutation.
- Evidence for activity in EGFR TKI naïve patients with uncommon EGFR mutations including the T790M is limited.

Patients must be adequately educated about the management of diarrhea and provided with loperamide when starting afatinib.

Since sunlight can exacerbate skin rash reactions, patients should be advised to avoid the sun or use adequate sun protection.

Adults:

Oral: 40 mg/day

Dosage with Toxicity:

Dose Level	Afatinib Dose (mg/day)
0	40
-1	30
-2	20
-3	Discontinue

Do not re-escalate previously reduced doses.

Refer to H – Interactions section for dosing recommendations when co-administered with P-gp inhibitors or inducers.

Note: The U.S. Prescribing Information suggests reducing afatinib dose by 10mg with P-gp inhibitors and monitoring for toxicity, and increasing afatinib dose by 10mg (as tolerated) when used with chronic concomitant P-gp inducer therapy. Then, reducing afatinib back to the original dose 2 to 3 days after discontinuing the P-gp inducer.

Table A: Dose Modifications for Toxicity Other than Diarrhea

Toxicity Grade	Action*
Grade 1 or 2	Maintain same dose
Prolonged (≥ 7 days) or intolerable grade 2 (including rash, nausea, vomiting and renal impairment) despite adequate symptomatic management** Or Grade 3 or 4**	Hold until ≤ grade 1 then restart at ↓ 1 dose level For skin reactions, consider referral to a specialist.
Keratitis	Hold and refer to ophthalmologist; consider discontinuation
Interstitial Lung Disease	Hold; investigate and treat patient appropriately. Discontinue if confirmed.

LVEF below institution's lower limit of normal Or Cardiac signs and symptoms	Hold and refer to cardiologist; consider discontinuation
Severe hepatic impairment during treatment	Discontinue
Gastrointestinal perforation	
Bullous, blistering or exfoliating skin conditions, suspected toxic epidermal necrolysis or Stevens-Johnson syndrome	

*Permanently discontinue afatinib for any toxicity not recovered to ≤ grade 1 within 14 days or if cannot tolerate 20 mg/day.

**Consider holding afatinib for worsening hepatic function; discontinue if severe hepatic impairment

Table B: Management of Diarrhea

Patients should have an adequate supply of loperamide readily available at the start of and during treatment.

Diarrhea Grade	Action
Any	Take 4mg (2 tablets) of loperamide immediately, followed by 2mg (1 tablet) with every loose bowel movement up to maximum daily dose of 20mg (10 tablets). Continue until resolved for ≥ 12 hours. Give oral hydration (1.5L/m^2/day plus equivalent of actual fluid loss) and electrolytes especially for ≥ grade 2. Hospitalize for IV fluids if patients becomes dehydrated. Avoid lactose containing products.
Grade 1 or Grade 2 < 48 hrs	Maintain same afatinib dose.
Grade 2 lasting ≥ 48 hours despite adequate anti-diarrheal treatment or Grade 3	Hold afatinib until grade ≤ 1 then restart at ↓ 1 dose level. Discontinue if not recovered to ≤ grade 1 within 14 days.
Grade 4	Discontinue

Dosage with Hepatic Impairment:

Similar exposure was observed in single-dose study in normal hepatic function versus mild/moderate hepatic impairment.

Hepatic Impairment	Afatinib Starting Dose / Action
Mild (Child Pugh A)	No dose adjustment required. Monitor closely for toxicity.
Moderate (Child Pugh B)	
Severe (Child Pugh C)	Do not treat

Dosage with Renal Impairment:

Higher exposure of afatinib was observed in renal impairment, which may increase the risk of developing adverse events. Monitor patients closely for toxicities.

CrCl (mL/min)	Afatinib Starting Dose
≥ 60	No adjustment required
30-59	No adjustment required; monitor for adverse reactions
15-29	30 mg daily
< 15 or on dialysis	Do not treat (not studied)

Dosage in the elderly:

No dose adjustment required. Elderly patients are more likely to experience severe adverse events, especially diarrhea. Monitor these patients closely for toxicities.

Dosage based on gender:

Higher exposure was observed in female patients as well as patients with lower body weight, which may increase the risk of developing adverse events. Monitor closely for toxicities.

Dosage based on ethnicity:

Population pharmacokinetic analysis suggests that race does not have a clinically important effect on afatinib exposure.

Children:

The safety and efficacy of afatinib has not been established in the pediatric population.

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F - Administration Guidelines

- Tablets should be swallowed whole with a glass of water and not crushed or chewed.
- Afatinib should be taken on an empty stomach, at least 1 hour before or 3 hours after eating.
- If a dose is missed, afatinib should be taken as soon as it is remembered. If there are less than 8 hours until the next scheduled dose, patients should skip the missed dose and take the next one as scheduled.
- If vomiting occurs after taking the dose, patients should not take a replacement tablet. The next dose should be taken at its scheduled time.
- Patients should have an adequate supply of loperamide readily available at the start of, and throughout therapy.
- Store at 15 - 30^{o}C.
- Blister card should be stored in the original package away from moisture and light;
- Only one pouch should be opened at a time. All the tablets in a blister card should be consumed, before opening a new one.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- Afatinib is not recommended for patients with:
  - Significant or recent gastrointestinal disorders with diarrhea as a major symptom (e.g. Crohn's disease, malabsorption or any other relevant disorder).
  - A history of interstitial lung disease
  - Severe hepatic or renal impairment
  - HER-2 positive metastatic breast cancer, in combination with vinorelbine, as increased adverse effects and increased mortality have been reported.
  - With hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption as afatinib tablets contains lactose.
- Use with caution in patients with:
  - Abnormal LVEF or those with significant cardiac history as afatinib has not been studied in these patient populations.
  - A history of keratitis, ulcerative keratitis, severe dry eye or those who use contact lenses.
- Blurred vision and keratitis have been observed; caution is required when driving or operating machinery.

Other Drug Properties:

- Carcinogenicity: Unknown
- Phototoxicity: Probable
  - Patients should be advised to avoid sun exposure or wear sufficient sun protection.

Pregnancy and Lactation:

- Mutagenicity: No
- Genotoxicity: No
- Embryotoxicity: Yes
  Afatinib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **2 weeks** after the last dose.
- Fetotoxicity: Yes
- Breastfeeding:
  Excretion into breast milk documented in animals.
  Breastfeeding is not recommended during treatment and for at least **2 weeks** after the last dose.
- Fertility effects: Probable

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H - Interactions

Drug-drug interactions due to inhibition or induction of CYP enzymes or UGT1A1 by concomitant medications are unlikely.

Although afatinib is a moderate inhibitor of Pgp in vitro, clinical data suggest the drug is unlikely to affect other Pgp substrates.

Smoking and alcohol consumption had no significant effects on afatinib pharmacokinetics, while food significantly decreased drug exposure (see Pharmacokinetics).

AGENT	EFFECT	MECHANISM	MANAGEMENT
P-glycoprotein inhibitors (i.e. quinidine, verapamil, cyclosporine, ritonavir) or BCRP inhibitors (i.e. ritonavir)	↑ afatinib exposure (up to 48% observed when P-gp/BCRP inhibitor given before afatinib)	↓ metabolism of afatinib	Avoid strong inhibitors if possible. If concomitant use is unavoidable, monitor for toxicity. Consider reducing afatinib dose if combination is not tolerated (See Dosing section).
P-glycoprotein inducers (i.e. rifampin)	↓ afatinib exposure (up to 34% observed)	↑ metabolism of afatinib	Avoid strong inducers. Consider adjusting afatinib dose for patients who require chronic therapy with a P-glycoprotein inducer (See Dosing section).
BCRP substrates (i.e. topotecan, rosuvastatin, sulfasalazine)	↑ exposure of BCRP substrates (theoretical)	afatinib is a BCRP inhibitor	Caution

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests	Baseline and at each visit; more frequently in patients with hepatic impairment
Renal function tests and electrolytes (especially in patients at high risk of dehydration)	Baseline and at each visit
LVEF for patients with cardiac risk factors or conditions that can affect LVEF.	Baseline and as clinically indicated
Clinical toxicity assessment of skin and nails, diarrhea, mucositis and other GI, respiratory, ophthalmic and cardiac effects and hypersensitivity/immune reactions	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- AFAtinib - For first-line monotherapy in patients with advanced or metastatic non-small cell lung cancer (NSCLC), according to specific criteria ()

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K - References

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April 2024 Updated pregnancy/breastfeeding section

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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