Drug Monograph

A - Drug Name

gefitinib

COMMON TRADE NAME(S): Iressa®

back to top

B - Mechanism of Action and Pharmacokinetics

Gefitinib is an orally active selective inhibitor of the epidermal growth factor receptor tyrosine kinase (EGFR-TK), an enzyme that regulates intracellular signalling pathways implicated in the proliferation and survival of cancer cells. EGFR is expressed on the cell surface of many normal cells as well as tumours such as lung, ovarian, breast and head and neck cancer. Activating mutations of EGFR have been described. This class of agents appears to have activity as a single agent in NSCLC, but only erlotinib has shown a survival benefit in randomized phase III studies (NCIC CTG BR.21 – erlotinib). For first-line NSCLC treatment, gefitinib increases progression-free survival as compared to paclitaxel-carboplatin, in patients with mutated EGFR. No difference in overall survival was observed.

Absorption	Exposure increases proportionally over the dosing range of 50-250 mg. Steady state is achieved in 7-10 days.	
	Bioavailability	60%. Bioavailability not significantly altered by food, but a significant sustained ↑ in gastric pH (such as with H2 antagonists or PPI) may reduce plasma concentrations of gefitinib.
Distribution	Gefitinib is extensively distributed throughout body tissues.	
	Cross blood brain barrier?	Yes (but low)
	PPB	Yes (90%)

Metabolism	Primarily metabolized in the liver via cytochrome P450 (CYP) 3A4; CYP2D6 is involved in the formation of the major metabolite. Poor CYP2D6 metabolizers achieved 2 times higher mean gefitinib exposure than extensive metabolizers.	
	Active metabolites	no
	Inactive metabolites	O-desmethyl gefitinib and others
Elimination	Excretion is predominantly via the feces (86%)	
	Urine	<4% of dose
	Half-life	31 - 41 hours (mean terminal t ½).

back to top

C - Indications and Status

Health Canada Approvals:

- Non-small cell lung cancer

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

Other Uses:

- Head and neck cancer

back to top

D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

Extravasation Potential: Not applicable

The following table contains adverse effects reported from the IPASS trial for the 250mg daily dose.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial thromboembolism	E
Dermatological	Abnormal eyelash growth	D
	Alopecia (11%)	E
	Cutaneous vasculitis (rare)	E
	Other - Skin fissures	E
	Paronychia (14%)	D
	Rash (52%) (may be severe)	E
Gastrointestinal	Anorexia (19%)	E D
	Constipation (12%)	E
	Diarrhea (47%) (may be severe)	E
	GI perforation (rare)	E
	Mucositis (13%)	E
	Nausea, vomiting (17%)	I
General	Fatigue (14%)	E
Hematological	Hemorrhage (4%) (may be severe)	E
	Myelosuppression (7%) (severe < 2%)	D
Hepatobiliary	↑ LFTs (11%) (may be severe)	E D
	Pancreatitis (rare)	E
Hypersensitivity	Hypersensitivity (rare)	I
Musculoskeletal	Musculoskeletal pain (8%)	E
Nervous System	Insomnia (15%)	E
	Neuropathy (4%)	E
Ophthalmic	Blepharitis (7%)	D
	Conjunctivitis (7%)	D
	Dry eye (7%) , keratitis (<1%, may be severe)	D
Renal	Creatinine increased (2%) (may be severe)	E
Respiratory	Cough, dyspnea (9%)	E
	Interstitial lung disease (1%)	D

* "*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)

Gefitinib was generally well-tolerated, with the most commonly reported effects being **gastrointestinal** (diarrhea, nausea and vomiting) and **skin changes** (rash, acne, dry skin, and pruritus).

Skin reactions (acneiform rash on face, scalp or chest) are common and usually mild to moderate, but may be severe. They usually appear by day 10 to 14 of treatment, may diminish with continued treatment, and are reversible when drug is withdrawn. In some patients the rash may be itchy or painful, cosmetically worrisome or associated with paronychiae, and usually be managed with a brief interruption of therapy.

Diarrhea is another frequently occurring adverse event; 1% of patients have grade 3 or 4 diarrhea, which may be associated with dehydration and should be managed appropriately. Problematic symptoms can also be managed by providing a brief therapy interruption.

Renal failure has been observed and is secondary to dehydration due to diarrhea, nausea/vomiting, anorexia, concurrent infections, or concurrent medications (e.g. chemotherapy).

Interstitial Lung Disease has been reported in 1% of patients receiving gefitinib, and may be fatal in up to a third of the cases. The reported incidence appears higher in Japan. The incidence may increase in patients with pre-existing ILD, a recent diagnosis of NSCLC (< 6 months) with poor PS, with concurrent heart disease, who are ≥ 55 years or are current smokers. If patients present with worsening of respiratory symptoms such as dyspnea, cough and fever, gefitinib should be interrupted and prompt investigation initiated.

Hemorrhages have been reported in 4% of patients but may be fatal, and usually involve gastrointestinal or respiratory systems. Rare, fatal cases of gastrointestinal perforation have been reported in patients with risk factors such as concomitant NSAIDs or steroids, history of GI ulcer, age, smoking, GI obstruction, advanced bowel disease and bowel metastases at perforation sites.

Corneal erosion is uncommon with gefitinib use and is reversible. Other generally mild **ophthalmic** symptoms such as conjunctivitis, blepharitis, abnormal eyelash growth and dry eye are commonly reported. Recent corneal surgery and contact lens wearing are independent risk factors for ocular toxicity. Patients should be instructed to seek medical attention promptly if any eye symptoms develop.

back to top

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.

Use only in patients with known EGFR mutations; clinical characteristics are not sufficient.

Adults:

Oral: 250mg once daily with or without food

Dosage with Toxicity:

Toxicity	Action
Grade 2 skin, eye toxicity, poorly tolerated diarrhea	Hold*, restart at 250mg daily when recovered
Grade 3 skin, eye toxicity, diarrhea, LFTs, dehydration	Hold*, may restart at 250mg daily when recovered
Grade 4 toxicities OR GI perforation OR treatment intolerance despite dose interruption	Discontinue
Keratitis	Hold and investigate. Consider discontinuing if ulcerative.
Pneumonitis	Hold in the presence of cough/dyspnea/fever and investigate. Discontinue if pneumonitis confirmed.

* up to 14 days for diarrhea and skin toxicity

Dosage with Hepatic Impairment:

Increased gefitinib exposure has been reported in patients with moderate and severe hepatic impairment due to cirrhosis. Dose adjustment is not required, but use with caution and monitor closely. Exercise caution in patients with mild to moderate changes in liver function; consider discontinuing gefitinib with severe changes in liver function.

Dosage with Renal Impairment:

No adjustment required in mild or moderate renal impairment. No specific recommendations were found for patients with severe renal impairment.

Dosage in the elderly:

No adjustment required.

Dosage in other populations:

No dose adjustment required based on gender, body weight, or ethnicity.

Children:

Safety and efficacy not established. May have increased risk of CNS bleeding.

back to top

F - Administration Guidelines

- Oral self-administration; drug available by outpatient prescription.
- May be administered with or without food.
- Avoid grapefruit, pomegranate, starfruit, Seville oranges, their juices or products during gefitinib treatment
- Missed dose should be taken as soon as possible, but only if there are at least 12 hours before the next dose is due. Otherwise, skip and take the next dose as scheduled.

back to top

G - Special Precautions

Contraindications:

- in patients with severe hypersensitivity to gefitinib or to any of its excipients
- EGFR mutation negative tumours

Other Warnings/Precautions:

- contains lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.
- risk of mortality among patients who develop ILD is higher in patients who are smokers, have pre-existing ILD, ≥ 65 years old, or have extensive areas adherent to the pleura.

Other Drug Properties:

- Carcinogenicity: Yes
  Gefitinib has potential phototoxic and contact sensitizing effects.

Pregnancy and Lactation:

- Genotoxicity: No
- Crosses placental barrier: Yes
- Fetotoxicity: Yes
- Pregnancy:
  Gefitinib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **6 months** after the last dose. (general recommendation)
- Excretion into breast milk: Yes
- Breastfeeding:
  Breastfeeding is not recommended during treatment.
- Fertility effects: Probable
  Documented in studies in female animals.

back to top

H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ gefitinib exposure (up to 83%), may ↓ efficacy	↑ metabolism of gefitinib	Caution; avoid co-administering with strong CYP3A4 inducers
CYP3A4 inhibitors (i.e. ketoconazole, voriconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges, starfruit or pomegranate)	↑gefitinib exposure (up to 80%)	↓ metabolism of gefitinib	Caution; avoid co-administering with strong CYP3A4 inhibitors
Proton pump inhibitors –PPI's (e.g. omeprazole etc.) and other drugs that increase gastric pH	↓ gefitinib exposure, may ↓ efficacy	↑ Gastric pH, reduces absorption	Caution
Coumadin (warfarin)	↑ anticoagulant effect	Unknown	Caution, monitor INR closely
Histamine H2-receptor antagonists (e.g. ranitidine, famotidine etc.)	↓ gefitinib exposure (47% by ranitidine), may ↓ efficacy	↑ gastric pH, reduces absorption	Caution
CYP2D6 substrates (e.g. beta-blockers, tramadol, nortriptyline, mirtazapine, serotonin-H3 antagonists)	↑ CYP2D6 substrate plasma concentration	gefitinib is a potentially mild inhibitor of CYP2D6 (In vitro)	None (clinically insignificant for metoprolol). Consider dose reduction for CYP2D6 substrates with narrow therapeutic index
Vinorelbine	Higher incidence of ≥ Grade 3 neutropenia	Synergistic effects	Avoid

back to top

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 routine
Electrolytes, creatinine and urea, especially in patients at high risk of dehydration	baseline and periodic
INR in patients on warfarin, especially initially, or when gefitinib is held or discontinued	Baseline and regular
Clinical assessments and grading of GI, skin, eye and respiratory symptoms	At each visit

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

back to top

J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- gefitinib - First-line monotherapy in locally advanced (not amenable to curative therapy) or metastatic NSCLC patients who have activating mutations of EGFR-TK, with specific criteria ()

back to top

K - References

Baselga J, Averbuch SD. ZD1839 (Iressa) as an anticancer agent. Drugs 2000;60 Suppl 1:33-40.

Culy CR, Faulds D. Gefitinib. Drugs 2002;62(15):2237-2248.

Kris MG, Natale RB, Herbst RS et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. JAMA 2003;290(16):2149-58.

Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361(10):947-57.

Product Monograph: Iressa® (Gefitinib). AstraZeneca Canada. September 27, 2012.

Shepherd FA, Rodrigues Pereira J, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353(2):123-32.

Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 2005;366:1527–37.

Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). Clin Oncol 2011;29(21):2866-74.

March 2025 Updated Pregnancy and Lactation section

back to top

L - Disclaimer

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

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an “as-is” basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information’s quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary’s content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person’s use of the information in the Formulary.

back to top