

DRUG NAME: Gefitinib**SYNONYM(S):** ZD1839**COMMON TRADE NAME(S):** IRESSA®**CLASSIFICATION:** epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Gefitinib is an inhibitor of epidermal growth factor receptor tyrosine kinase (EGFR-TK). It binds to ATP and prevents autophosphorylation and kinase activation. This results in inhibition of proliferation and angiogenesis, and induction of apoptosis.¹⁻³

PHARMACOKINETICS:

Interpatient variability	54% for steady state trough concentration	
Oral Absorption	60% bioavailability; not significantly altered by food; bioavailability reduced by 47% when gastric pH >5	
	time to peak plasma concentration	3-7 h
Distribution	extensively distributed	
	cross blood brain barrier	no information found
	volume of distribution	1400–1600 L
	plasma protein binding	90% (serum albumin and α_1 -acid glycoprotein); not concentration dependent
Metabolism	extensive hepatic metabolism via CYP3A4	
	active metabolite(s)	O-desmethyl gefitinib (1/14 the potency of gefitinib)
	inactive metabolite(s)	yes
Excretion	fecal and urinary excretion	
	urine	<4%
	feces	86% ³
	terminal half life	30.5–41 h
	clearance	500 mL/min
Gender	no information found	
Elderly	no clinically significant difference	
Children	no information found	
Ethnicity	no information found	

Adapted from standard reference¹ unless specified otherwise.**USES:****Primary uses:***Lung cancer, non-small cell¹⁻³**Other uses:**Head and neck⁴

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Use with caution in patients with hepatic impairment,^{1,3} idiopathic pulmonary fibrosis,^{1,3} and those at risk for QT interval prolongation.¹ Gefitinib is cleared primarily by the liver; therefore, gefitinib exposure may be increased in patients with hepatic dysfunction. However, it was shown that following gefitinib 250 mg daily in patients with moderate to severe hepatic dysfunction due to liver metastases, gefitinib pharmacokinetics (time to steady state, total plasma clearance or steady state concentration) were similar for the groups with normal and impaired hepatic function.¹ The influence of non-cancer related hepatic impairment (due to cirrhosis or hepatitis) on the pharmacokinetics of gefitinib has not been evaluated.¹

Carcinogenicity: Carcinogenicity studies have not been conducted with gefitinib.^{1,3}

Mutagenicity: Not mutagenic in mammalian *in vitro* mutation test. Not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.¹

Fertility: Animal studies have shown a reduction in female fertility at a dose of 20 mg/kg/day.¹

Pregnancy: FDA Pregnancy Category D.^{2,3} 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).

Breastfeeding is not recommended. Animal studies have shown levels of gefitinib and its metabolites were 11- to 19-fold higher in milk than in blood.¹

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. When placebo-controlled trials are available, adverse events will generally be included if the incidence is $\geq 5\%$ higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
blood/bone marrow febrile neutropenia	thrombocytopenia (severe 1%)
cardiovascular (arrhythmia)	atrial fibrillation (severe 1%)
	bundle branch block (severe 1%)
	QT prolongation
cardiovascular (general)	angioedema (<0.01%)
	peripheral edema (severe 1%)
constitutional symptoms	weight loss (2-3%)
dermatology/skin	acne (13-25%, severe 0%)
	alopecia (1-10%)
	dry skin (13-27%)
	epidermal necrolysis (<0.1%)
	erythema multiforme (<0.1%)
	exfoliative dermatitis (4-8%,severe 0%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	nail disorder (4%, severe 0%)
	pruritus (8-30%, severe 0%)
	rash (43-47%, severe 1%)
	seborrhea (6%, severe 1%)
	urticaria (<0.01%)
gastrointestinal	<i>emetogenic potential: low moderate</i>
	anorexia (7-9%, severe 0%)
	constipation (severe 1%)
	dehydration (1-10%, severe 1%)
	diarrhea (40-48%, severe 1%)
	mouth ulceration (1%) ³
	nausea (13%, severe 1%)
	pancreatitis (<0.1%)
	rectal disorder (severe 1%)
	stomatitis (8%)
	vomiting (6-12%, severe 1%)
hemorrhage	epistaxis (2%, severe 1%)
	hematuria (6%)
	other sites (rare)
hepatic	alkaline phosphatase increase (severe 1%)
	ALT/SGPT increased (1-13%, severe 1.9%)
	AST/SGOT increased (1-11%, severe 0%)
musculoskeletal	asthenia (6-8%, severe 1%)
ocular/visual	blepharitis (1-5%)
	conjunctivitis (1-4%)
	corneal erosion (<1%)
pain	abdominal pain (3%)
	pain (2-10%)
pulmonary	dyspnea (severe 1%)
	interstitial lung disease (0.3 -2%)
renal/genitourinary	scrotal edema (severe 1%)

Adapted from references^{1,3} unless specified otherwise.

Interstitial lung disease (ILD) is rare (0.3 – 2%), but potentially fatal.¹⁻³ Patients often present with acute onset of dyspnea, at times accompanied by cough or low-grade fever, usually becoming severe within a short time and requiring hospitalization.¹⁻³ Risk factors of fatal outcome from ILD include concurrent idiopathic pulmonary

fibrosis/interstitial pneumonitis/pneumoconiosis/ radiation pneumonitis/drug-induced pneumonitis.¹ Management of confirmed ILD includes discontinuation of gefitinib.¹⁻³

QT interval prolongation has been observed.¹ The clinical significance of these findings is not clear. Caution is advised when using gefitinib, especially in patients:¹

- known to be at risk of developing QT interval prolongation (e.g. hypokalemia, hypomagnesemia, bundle branch block, sinus node dysfunction)
- co-administered drugs known to induce QT interval prolongation
- co-administered drugs known to inhibit gefitinib metabolism
- with a known baseline QT interval >460 msec

Asymptomatic increases in liver transaminases have been observed in gefitinib-treated patients; therefore, periodic liver function testing is recommended. Caution is advised when using gefitinib in the presence of mild to moderate increases in liver transaminases. Discontinuation should be considered if changes are severe.^{1,3}

General intolerance:

- *poorly tolerated diarrhea or skin reactions:* may be managed with a brief (up to 14 days) interruption of therapy. Reinstate the 250 mg daily dose once toxicity has resolved.¹⁻³
- *ocular symptoms:* should have therapy interrupted and symptoms evaluated. Consider reinstating the 250 mg daily dose once toxicity has resolved.¹⁻³
- *acute onset or worsening of respiratory symptoms:* should have gefitinib therapy interrupted and prompt investigation initiated. If interstitial lung disease is confirmed, discontinue gefitinib.¹⁻³

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit or grapefruit juice ⁵	may increase plasma level of gefitinib; effect may be related to dose and exposure	may inhibit CYP3A4 metabolism of gefitinib in the intestinal wall	avoid grapefruit or grapefruit juice
histamine H ₂ -receptor antagonists (e.g. ranitidine, famotidine, cimetidine), proton pump inhibitors	may decrease plasma level of gefitinib	sustained elevation of gastric pH	use with caution
itraconazole ^{6,7}	increases plasma level of gefitinib	inhibits CYP3A4 metabolism of gefitinib	use with caution
metoprolol ¹	metoprolol level increased by 30 to 35%	decreased CYP2D6 metabolism of metoprolol	none (clinically non-significant)
rifampin ^{6,7}	decreases plasma level of gefitinib	induces CYP3A4 metabolism of gefitinib	an increase in gefitinib dose has been suggested ^{2,3} ; however, the clinical significance of doing this is unclear ⁸
warfarin	enhanced anticoagulant effect	unknown	monitor PT or INR closely

Adapted from reference⁷ unless specified otherwise.

CYP3A4 inhibitors may decrease metabolism and increase gefitinib plasma concentrations. Concurrent administration of drugs that inhibit CYP3A4 (eg, ketoconazole, clarithromycin, erythromycin, protease inhibitors) may significantly increase exposure to gefitinib.⁷

CYP3A4 inducers may increase metabolism and decrease gefitinib plasma concentrations. Concurrent administration of drugs that induce CYP3A4 (eg, carbamazepine, phenytoin, barbiturates, St. John's Wort) may significantly reduce exposure to gefitinib.⁷

SUPPLY AND STORAGE:

Tablets: 250 mg; store at room temperature.

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:

BCCA usual dose noted in ***bold, italics***

<i>Oral:</i>	<i>250 mg PO once daily.</i> May be taken with or without food. ¹⁻³
<i>Dosage in renal failure:</i>	no adjustment required
<i>Dosage in hepatic failure:</i>	no adjustment required for hepatic failure due to liver metastases severe increases in liver transaminases warrant discontinuation of gefitinib ¹
<i>Dosage in elderly</i>	no adjustment required
<i>Dosage in dialysis</i>	no information found

REFERENCES:

1. AstraZeneca Canada. IRESSA® Product Monograph. Mississauga, Ontario; 2003.
2. McEvoy G editor. AHFS Drug Information. Bethesda, MD: American Society of Health-System Pharmacists; 2004.
3. AstraZeneca UK. IRESSA® Product Insert. Cheshire, England; 2003.
4. Cohen EE, Rosen F., Stadler W.M., et al. Phase II trial of ZD1839 in recurrent or metastatic squamous cell carcinoma of the head and neck. *J Clin Oncol* 2003;21(10):1980-87.
5. AstraZeneca Canada Inc. IRESSA® product monograph. Mississauga, Ontario; 27 September 2012.
6. Swaisland H, Smith R, Farebrother J, et al. The effect of the induction and inhibition of CYP3A4 on the pharmacokinetics of single oral doses of ZD1839 ('IRESSA®'), a selective epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), in healthy male volunteers. *Proceedings of the American Society of Clinical Oncology* 2002;21:83a (abstract 328).
7. Repchinsky C editor. *Compendium of Pharmaceuticals and Specialties*. Ottawa, Ontario: Canadian Pharmacists Association; 2005.
8. Nevin Murray MD. Personal Communication. BC Cancer Agency Lung Tumor Group; 25 October 2004.