

[Drug Name](#) | [Mechanism of Action & Pharmacokinetics](#) | [Indications & Status](#) | [Adverse Effects](#) | [Dosing](#) | [Administration Guidelines](#) | [Special Precautions](#) | [Interactions](#) | [Recommended Clinical Monitoring](#) | [References](#)

A DRUG NAME: ERLOTINIB

SYNONYM(S): OSI-774, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, CP-358,774

COMMON TRADE NAME(S): Tarceva® (Roche Canada)

B MECHANISM OF ACTION AND PHARMACOKINETICS

Erlotinib is a selective epidermal growth factor receptor tyrosine kinase inhibitor. Activation of epidermal growth factor receptors (EGFR) results in a cascade of intracellular signalling events, leading to cell proliferation, differentiation, cell survival, angiogenesis, and invasion/metastases. These receptors are overexpressed in NSCLC and other tumor types, and may be correlated with more aggressive tumor activity and poor clinical outcome. Erlotinib inhibits the intracellular phosphorylation of tyrosine kinase associated with the EGFR. Many studies suggest that EGFR mutations, EGFR FISH expression and RAS mutations may be important predictors of EGFR activity.

Oral Absorption	60% (↑ with food)
Distribution	Peak plasma levels of erlotinib occur 4 hours after an oral dose in cancer patients. Steady state is achieved in 7-8 days.
	Cross blood brain barrier? Yes
	PPB 95% (albumin and AAG)
Metabolism	Hepatic primarily via CYP3A4, and to a lesser extent via CYP1A2 and the extrahepatic isoform CYP1A1.
	active metabolite(s) Yes (primarily OSI-420)
	inactive metabolite(s) Unknown
Excretion	Excretion is predominantly via the feces (>90%).
	Urine < 9% (< 1% unchanged)
	t _{1/2} (mean) 36.2 hours

▲ [Back to Top](#)

C INDICATIONS AND STATUS

*Erlotinib is indicated as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen, and whose EGFR expression status is positive or unknown.

Advanced pancreatic cancer: 100mg erlotinib in combination with gemcitabine

* Health Canada approved indication

▲ [Back to Top](#)

D ADVERSE EFFECTS (Monotherapy or in combination)			
ORGAN SITE	SIDE EFFECT*	ONSET**	
Cardiovascular	Myocardial ischemia/infarction (<1%)	E	
	Arterial/venous thromboembolism	E	
	Arrhythmia, syncope (rare)	E	
Neurological	Neuropathy (1%)	E	
	Anxiety (1%)	E	
Dermatologic	<u>Rash /acne (75%), may be severe</u>	E	
	<u>Hyperpigmentation (< 1%)</u>	E	
	Nail changes (1-10%) including paronychia	E	
	Alopecia/hirsutism (<1%)	E	D
	Pruritus (13%), Dry skin (12%)	E	
	Phototoxicity (radiation induced)	E	
Gastrointestinal	<u>Diarrhea (54%) (Grade 3 or 4 - 6%)</u>	E	
	Nausea, vomiting (33%)	E	
	Pancreatitis, ileus, flatulence	E	
	Stomatitis (17%)	E	
	Anorexia (52%), abdominal pain (11%)	E	
	Gastrointestinal bleeding (2%), perforation (rare)	E	
Pulmonary	Interstitial Lung Disease (1%)	E	D
	Dyspnea, cough (41%)	E	D
Generalized	Infection (24%)	E	
	Microangiopathic hemolytic anemia (rare)	E	
	Fever, bone pain (gemcitabine combination)	E	
	Fatigue (52%)	E	
	Headache, dizziness (<1%)	E	
Hepatic, Renal	Renal failure, hepatorenal	E	
	↑ LFTs (4%)	E	D
Ocular	Conjunctivitis (12%)	D	
	Keratoconjunctivitis sicca (12%)	D	
	Abnormal eyelash growth	D	
	Keratitis, corneal erosion/perforation (rare)	D	
Metabolic	Hypokalemia (rare)	E	

* Dose-limiting side effects are underlined.

** I = immediate (onset in hours to days)

E = early (days to weeks)

D = delayed (weeks to months)

L = late (months to years)

D

ADVERSE EFFECTS (cont.)

The most frequent adverse effects associated with erlotinib are **acneiform-like skin rash** and **diarrhea**.

Mild to moderate erythematous or papulopustular **rash** typically involves the face and upper trunk. It usually occurs after 8-10 days, and may worsen in sun-exposed areas. Use of protective clothing and/or sunscreen is suggested before sun exposure. Treatment of the rash with retinoids, vitamin A or D, or steroids did not generally shorten the course. Treatment with minocycline, topical silver sulfadiazine, (Adjei, 2001) or tetracycline may reduce the severity, but not the incidence of skin rashes.

Diarrhea is common, may be moderate or severe and loperamide should be used. Severe diarrhea may result in dehydration and renal failure. In patients with severe or persistent case of diarrhea, nausea, anorexia, or vomiting associated with dehydration, interrupt erlotinib and treat appropriately.

Liver function test abnormalities may be symptomatic, and are usually transient and reversible. However, fatal hepatotoxicity has occurred in patients with moderate hepatic impairment receiving erlotinib; such patients should be closely monitored and dose modification considered.

Infrequent cases of serious and life-threatening **gastrointestinal bleeding** have been reported in clinical studies; some are associated with a history of ulcer disease, concomitant warfarin administration (see [Section H – Interactions](#)) and some with concomitant NSAID administration. Regular monitoring of prothrombin time or international normalized ratio is advised for patients treated with concomitant warfarin (or coumarin- derived agents) and erlotinib. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane-based chemotherapy, or have a history of gastric ulcers or diverticular disease are at increased risk of gastrointestinal perforation.

Recent cataract surgery or contact lens wearing are risk factors for corneal ulceration/perforation while on erlotinib therapy.

There have been infrequent reports of **Interstitial Lung Disease** (including fatalities). Pulmonary symptoms appeared from 5 days to more than 9 months (median 47 days) after initiation of erlotinib. In most cases, there were associated contributing factors (concomitant/prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections). Patients with respiratory symptoms should have erlotinib held pending diagnosis and permanently discontinued if proven to be ILD.

▲ [Back to Top](#)

E

DOSING

Refer to protocol by which patient is being treated.

Adults: The recommended daily dose of Erlotinib is 150 mg taken at least one hour before or two hours after the ingestion of food. When dose reduction is necessary, the erlotinib dose should be reduced in 50 mg decrements. There is no evidence that treatment beyond progression is beneficial.

E DOSING (continued)Dosage Modifications:

Toxicity	Action
<ul style="list-style-type: none"> Diarrhea 	Manage with loperamide. If severe, associated with dehydration or unresponsive to loperamide, hold and/or reduce dose.
<ul style="list-style-type: none"> Patients with dehydration at risk of renal failure Acute/new or worsening ocular disorders 	Hold or discontinue
<ul style="list-style-type: none"> Acute/new or worsening pulmonary symptoms (e.g. dyspnea, cough, fever) 	Hold; investigate and treat appropriately. Discontinue if ILD confirmed
<ul style="list-style-type: none"> GI bleeding/perforation Severe bullous, blistering or exfoliating rashes 	Discontinue; treat patient appropriately

Concomitant potent CYP3A4 inhibitor: Consider dose reduction in presence of adverse effects if severe. ([Section H: Interactions](#))

Dosage with renal impairment: Not significantly renally excreted. No dose adjustment required (Miller et al).

Dosage with hepatic impairment: Use with caution in combination with other hepatotoxic drugs.

Hepatic Impairment	Bilirubin		Transaminases	Action
Mild	< 1.5 x ULN	and	1-2.5 x ULN	100% , caution
Moderate	1.5-3 x ULN	and/or	2.5-5 x ULN	Caution; consider ↓. If worsens, hold then ↓ 50% or discontinue
Severe	> 3 x ULN (or 2 x baseline values)	or	> 5 x ULN (or 3 x baseline values)	Discontinue

Dosage in the elderly: No adjustment required.

Children: Safety and efficacy not established.

▲ [Back to Top](#)

F ADMINISTRATION GUIDELINES (see [Appendix 3a](#))

- Oral self-administration; drug available by outpatient prescription.
- Should be administered at least one hour before or two hours after meal.

▲ [Back to Top](#)

G SPECIAL PRECAUTIONS

Erlotinib is contraindicated in patients with severe hypersensitivity reactions to erlotinib or any of its components. Erlotinib contains lactose and should not be used in patients with hereditary lactase/glucose or galactose disorders.

The concomitant use of erlotinib with potent inducers of cytochrome P-450 (CYP) isoenzyme 3A4 (e.g. rifabutin, rifampin, rifapentin, phenytoin, carbamazepine, phenobarbital, St. John's wort) should be avoided. ([Section H – Interactions](#))

Patients on oral anticoagulants should be closely monitored when doses of erlotinib are started, modified or discontinued.

Monitor hepatic function closely in patients with pre-existing liver disease or on concomitant hepatotoxic medications. The Child-Pugh criteria may have limitations in advanced cancer patients with liver involvement.

It is not known whether erlotinib is **carcinogenic**. In animal studies, erlotinib crosses the placenta and is **fetotoxic**, but is not mutagenic, clastogenic, teratogenic nor does it impair **fertility**. Women of childbearing potential should be advised to avoid becoming **pregnant** while receiving treatment of erlotinib. Adequate contraceptive methods should be used during therapy and for at least 2 weeks after completing treatment. It is not known whether erlotinib is excreted in human milk. Since many drugs are excreted in human milk and because the effects of erlotinib on infants have not been studied, women should be advised against **breast-feeding** while receiving erlotinib therapy.

▲ [Back to Top](#)

H INTERACTIONS

AGENT	EFFECT	MECHANISM	MANAGEMENT
Potent CYP3A4 inducers (e.g. phenytoin, carbamazepine, nevirapine, rifampicin, barbiturates, or St John's Wort, etc.)	↓ Erlotinib plasma concentration and ↓ efficacy	Effects on CYP 3A4, ↑ Erlotinib metabolism	Avoid concomitant administration
Potent CYP3A4 ± CYP1A2 inhibitors (e.g. diltiazem, ritonavir, ketoconazole, erythromycin, protease inhibitors, ciprofloxacin, grapefruit juice, etc.)	↑ Erlotinib plasma concentration and ↑ toxicity	Effects on CYP 3A4, ↓ Erlotinib metabolism	Avoid concomitant administration, ↓ erlotinib dose with severe toxicity
Coumadin	↑ anticoagulant effect	Unknown	Caution, monitor INR closely

H	INTERACTIONS (Continued)			
	AGENT	EFFECT	MECHANISM	MANAGEMENT
	Proton pump inhibitors	↓erlotinib exposure (AUC, Cmax)	Solubility of erlotinib ↓ as pH ↑	Avoid concomitant usage; use antacid instead (≥ 2 hrs prior to or after erlotinib)
	Cigarette smoking	↓ erlotinib exposure (by 50-60%)	↑ clearance	Encourage smoking cessation

▲ [Back to Top](#)

I	RECOMMENDED CLINICAL MONITORING	
	Recommended Clinical Monitoring	Suggested Clinical Monitoring
	<ul style="list-style-type: none"> • Baseline and routine liver function tests; monitor closely if abnormal. Grade toxicity using the current NCI Common Toxicity Criteria Version • Regular clinical assessments and grading of diarrhea, skin/nails, stomatitis, eye symptoms and respiratory symptoms • Close monitoring of INR in patients on warfarin, especially initially, or when dose modified, held, or discontinued • Baseline and routine renal function, electrolytes in patients at high risk of dehydration 	

▲ [Back to Top](#)

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▲ [Back to Top](#)