Drug Monograph

A - Drug Name

erlotinib

COMMON TRADE NAME(S): Tarceva®

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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, or mutated with constitutive activation, in NSCLC and other tumor types, and may be correlated with more aggressive tumor activity and poor clinical outcome. Continued cigarette smoking significantly reduces exposure. The safety and efficacy of higher doses in such patients has not been established.

Absorption	Bioavailability	oral : 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 metabolites	Yes (primarily OSI-420).
	Inactive metabolites	Unknown

Elimination	Excretion is predominantly via the feces (>90%).	
	Urine	< 9% (< 1% unchanged)
	Half-life	(mean) : 36.2 hours

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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 of approved indications.

Other Uses:

- Vulvar cancer
- Head and neck cancer

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

Extravasation Potential: Not applicable

The following table contains adverse effects reported in the BR21 trial where the incidence was greater than placebo, or severe events from other trials.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Venous thromboembolism (4%)	E
Dermatological	Abnormal eyelash growth	D
	Nail disorder (16%) (including paronychia)	E
	Photosensitivity (phototoxicity; radiation induced)	E
	Rash (75%) (or acne; may be severe)	E
	Skin discolouration (<1%)	E

Gastrointestinal	Abdominal pain (11%)	E
	Anorexia, weight loss (52%)	E
	Diarrhea (54%) (grade 3: 4%)	E
	GI hemorrhage (2%)	E
	GI perforation (rare)	E
	Mucositis (17%)	E
	Nausea, vomiting (33%)	E
General	Fatigue (52%)	E
Hematological	Hemolysis (rare)	E
	Myelosuppression (11%) (usually mild)	E
Hepatobiliary	↑ LFTs (6%) (may be severe)	E
Infection	Infection (24%)	E
Musculoskeletal	↑CPK (rhabdomyolysis with statins)	E
Ophthalmic	Conjunctivitis (12%) /uveitis	D
	Corneal disorder (12%) (ulcer/perforation)	D
Renal	Nephrotoxicity (may be severe)	E
Respiratory	Cough, dyspnea (45%)	E D
	Pneumonitis (1%) /fibrosis	E 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)

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 , electrolyte abnormalities, 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 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.

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E - Dosing

Refer to protocol by which patient is being treated. EGFR mutation-positive status must be confirmed with a validated test prior to staring erlotinib therapy for first line and maintenance settings.

Adults:

The recommended daily dose of erlotinib is 150 mg taken at least one hour before or two hours after the ingestion of food.

Dosage with Toxicity:

Dose levels 150mg, 100mg, 50 mg

Toxicity	Action
• Diarrhea	Manage with loperamide. If severe, associated with dehydration or unresponsive to loperamide, hold and/or reduce dose.
• Patients with dehydration at risk of renal failure • Acute/new or worsening ocular disorders	Hold or discontinue
• Acute/new or worsening pulmonary symptoms (e.g. dyspnea, cough, fever)	Hold; investigate and treat appropriately. Discontinue if ILD confirmed
• GI bleeding/perforation • Severe bullous, blistering or exfoliating rashes • Rhabdomyolysis • ≥ grade 3 LFTs	Discontinue; treat patient appropriately
• Other grade 3 or 4 toxicity	Reduce by one dose level especially if being administered with potent CYP3 A4 inhibitors

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)	Do not treat

Dosage with Renal Impairment:

Not significantly renally excreted. No dose adjustment required if no concomitant hepatic dysfunction (Miller et al).

Dosage in the elderly:

No adjustment required.

Children:

Safety and efficacy not established.

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F - Administration Guidelines

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

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G - Special Precautions

Contraindications:

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

Other Warnings/Precautions:

- Erlotinib has not been studied in patients with severe hepatic or renal impairment.
- The concomitant use with potent inducers of cytochrome P-450 (CYP) isoenzyme 3A4 (e.g. rifabutin, rifampin, rifapentin, phenytoin, carbamazepine, phenobarbital, St. John's wort), PPIs and statins should be avoided. (See Interactions).
- Patients on oral anticoagulants should be closely monitored when doses of erlotinib are started, modified or discontinued.
- Contains lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption

Pregnancy and Lactation:

- Mutagenicity: Unlikely
- Clastogenicity: Unlikely
- Teratogenicity: Unlikely
- Fetotoxicity: Documented in animals
  Erlotinib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **2 weeks** after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended during treatment and for at least **2 weeks** after the last dose.
- Fertility effects: Unlikely

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H - Interactions

Erlotinib is metabolized by CYP3A4 and to a lesser extent by CYP1A2 and is therefore susceptible to drug interactions with inducers and inhibitors of these isoenzymes.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ Erlotinib plasma concentration and decreased efficacy	↑ metabolism of erlotinib, effects on CYP3A4	Avoid concomitant administration of potent inducers
Potent CYP3A4 ± CYP1A2 inhibitors (e.g. diltiazem, ritonavir, ketoconazole, erythromycin, protease inhibitors, ciprofloxacin, grapefruit juice, etc.)	↑ Erlotinib plasma concentration and increased toxicity	↓ metabolism of erlotinib, effects on CYP3A4	Avoid concomitant administration, decrease erlotinib dose with severe toxicity
Warfarin	↑ anticoagulant effect	Competes for CYP3A4/A5 binding sites	Caution, monitor INR closely
Drugs that increase gastric pH (Proton pump	↓ erlotinib exposure (AUC, Cmax)	Solubility of erlotinib decreases as pH increases	Avoid concomitant usage; consider using H2-antagonist (take

inhibitors, H2-antagonists, antacids)			erlotinib 2 h prior to AM dose or 10 h after PM dose)
Statins (e.g., atorvastatin, pravastatin, simvastatin, etc.)	↑ statin-induced myopathy (including rhabdomyolysis)		Monitor liver function tests in patients with liver impairment
Cigarette smoking	↓ erlotinib exposure (by 50-60%)	↑ clearance via CYP1A2 induction	Encourage smoking cessation

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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.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Renal function tests, including electrolytes	Baseline and routine
Close monitoring of INR, in patients on warfarin	Especially initially, or when dose modified, held, or discontinued
Liver function tests	Baseline and routine, monitor closely if abnormal.
Clinical assessments and grading of diarrhea, skin/nails, stomatitis, thromboembolism, infection, eye symptoms and respiratory symptoms.	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)

- erlotinib - Incurable progressive NSCLC, with specific criteria

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K - References

Adjei AA: Epidermal growth factor receptor tyrosine kinase inhibitors in cancer therapy. Drug Future 2001; 26(11):1087.

E- American Society of Health-System Pharmacists. 2005: Erlotinib.

Herbst RS, Prager D, Hermann R et al. TRIBUTE - A phase III trial of erlotinib HCl (OSI-774) combined with carboplatin and paclitaxel (CP) in advanced non-small cell lung cancer (NSCLC). J Clin Oncol 2005; 23(25): 5892-9.

Hidalgo M, Siu LL, Nemunaitis J et al: Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. J Clin Oncol 2001; 19(13): 3267-3279.

Erlotinib: e-Drugdex Evaluations. Micromedex Healthcare Series.

Jatoi A, Rowland A, Sloan JA, et al. Tetracycline to prevent epidermal growth factor receptor inhibitor-induced skin rashes: results of a placebo-controlled trial from the north central cancer treatment group (N03CB). Cancer 2008; 113:847–53.

Micromedex review: Erlotinib

Micromedex P&T Quick Report: Erlotinib.

Miller AA, Murry DJ, Owzar K, et al. Phase I and pharmacokinetic study of erlotinib for solid tumors in patients with hepatic or renal dysfunction: CALGB 60101. J Clin Oncol 2007; 25: 3055-60.

Product monograph: Tarceva® (erlotinib). Hoffman-La Roche Ltd, Canada, March 2017.

Prescribing information: Tarceva® (erlotinib). Genentech Inc. U.S., April 2009.

Shepherd F, Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non–small-cell lung cancer. NEJM 2005; 353(2): 123-132.

Vogelbaum MA, Peereboom D, Stevens GH, et al. Phase II study of single agent therapy with the EGFR tyrosine kinase inhibitor erlotinib in recurrent glioblastoma multiforme. Proceedings from the 29th ESMO Congress, Vienna, Austria, October 29 – November 3, 2004; (Abstract #783).

October 2022 Updated Indications, Pregnancy/lactation sections

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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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