DRUG NAME: Erlotinib

SYNONYM(S): OSI-774

COMMON TRADE NAME(S): TARCEVA®

CLASSIFICATION: epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor[1]

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Erlotinib is an EGFR-specific tyrosine kinase inhibitor.[1] It inhibits EGFR autophosphorylation and therefore EGF-dependent cell proliferation. Erlotinib blocks cell-cycle progression in the G1 phase. Specificity with regard to other tyrosine kinase inhibitors is unknown.[2]

PHARMACOKINETICS:

Interpatient variability	24% higher clearance rate in smokers lower clearance rate associated with increased bilirubin and α_1-acid glycoprotein no clinically significant differences observed for different body weights	
Oral Absorption	pH-dependent solubility[3,4]; 59% bioavailability food may increase bioavailability to almost 100%,[5] but highly variable[6]	
	time to peak plasma concentration	4 h
Distribution	extensively distributed, including tumour tissues	
	cross blood brain barrier?	not fully characterized, but preliminary studies show efficacy in glioblastoma multiforme[7] and malignant glioma[8]
	volume of distribution	232 L
	plasma protein binding	95% (albumin and α_1-acid glycoprotein)
Metabolism	80-95% hepatic metabolism by CYP3A4 also metabolized by hepatic CYP1A2 and pulmonary isoform CYP1A1	
	active metabolite(s)	OSI-420 (O-demethylated metabolite)[9]
	inactive metabolite(s)	no information found
Excretion	predominantly in bile	
	urine	< 9%
	feces	> 90%
	terminal half life	36.2 h
	clearance	4.47 L/h
Gender	no clinically significant differences observed	
Elderly	no clinically significant differences observed	
Children	no information found	
Ethnicity	no clinically significant differences observed	

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:
*Lung cancer, non-small cell

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Contraindications: Erlotinib tablets contain lactose and should not be administered to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.[5]

Carcinogenicity: Erlotinib has not been tested for carcinogenicity.[1,5]

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation test.[3] Erlotinib is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[3]

Fertility: Animal studies show embryotoxicity, but not impaired fertility, teratogenicity, or abnormal pre- or postnatal physical or behavioural development.[1]

Pregnancy: FDA Pregnancy Category D.[5] 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 due to the potential secretion into breast milk.[1]

Use with caution in patients with pre-existing parenchymal lung disease or pulmonary infections.[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.[10]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
coagulation	***INR elevations, bleeding events***
constitutional symptoms	***fatigue*** (52%, severe 18%)
	weight loss (12%)[11]
dermatology/skin	dry skin (12%)
	erythema (18%)[11]
	hair changes (<1%)[3]; including hirsutism and eyelash/eyebrow changes[3]
	nail changes (<10%)[3]; including paronychia and brittle and loose nails[3]
	pruritis (13%)
	rash (75%, severe 9%)[1]; see paragraph following **Side Effects** table
gastrointestinal	*emetogenic potential: rare*
	anorexia (52%, severe 9%)
	diarrhea (54%, severe 7%)[1]; see paragraph following **Side Effects** table
	dyspepsia (12%)[11]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	dysphagia (12%)[11]
	nausea (33%)
	stomatitis (17%)
hemorrhage	***gastrointestinal hemorrhage*** (2%)
hepatic	***increases in liver transaminases*** (1-10%)[1,12]
infection	infection (24%, severe 4%)
neurology	anxiety (21%)[11]
	depression (16%)[11]
	insomnia (12%)[11]
ocular/visual	***conjunctivitis*** (12%, severe < 1%)
	keratoconjunctivitis sicca (12%)
pain	arthralgia (14%)[11]
	headache (17%)[13]
respiratory, thoracic and mediastinal	***dyspnea*** (41%, severe 28%)
	interstitial lung disease (0.6%)[1]; see paragraph following **Side Effects** table
syndromes	hepatorenal syndrome[12]

Adapted from standard reference[1] unless specified otherwise.

Rash is the most common side effect of erlotinib therapy. Generally a mild to moderate papulopustular rash, primarily on the face, neck, and upper torso, it usually occurs during the first two weeks of treatment.[14] Management is not standardized and is largely based on anecdotal evidence. To promote maximal skin hydration, general measures should include washing with tepid water and application of non-greasy, alcohol-free emollients.[15] Anti-acne or anti-rosacea agents should be avoided; they have variable efficacy and their drying properties may exacerbate dry skin. Sun exposure should be minimized as it may increase the incidence of hyperpigmentation and rash severity on unprotected areas of the skin. The use of sun blocking creams should be encouraged. [15-18] Patients with severe skin reactions may require a dose reduction or temporary interruption of therapy.[1]

Moderate or severe diarrhea should be treated with loperamide.[1] The suggested regimen is 4 mg at first onset, then 2 mg every 2-4 hours until diarrhea-free for 12 hours.[14] In some cases, erlotinib dose reduction may be necessary.[1] In the event of severe or persistent diarrhea, nausea, anorexia, or vomiting associated with dehydration, erlotinib therapy should be interrupted and appropriate measures should be taken to treat the dehydration.

Interstitial lung disease (ILD) is rare, but potentially fatal.[1] In one pivotal trial, the incidence of serious ILD was 0.8% in both the erlotinib arm and the placebo arm; the overall incidence is 0.6%. ILD may present 5 days to more than 9 months after initiating erlotinib, and may be diagnosed as pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome, or lung infiltration. Most cases are associated with confounding factors such as prior chemotherapy or radiotherapy, pre-existing lung disease, or pulmonary infections. Erlotinib therapy should be discontinued if ILD is diagnosed, and put on hold if ILD is suspected.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
antacids, H_2 blockers, or proton pump inhibitors[3]	reduced AUC and C_{max} of erlotinib ; may reduce pharmacological effect of erlotinib	pH-dependent solubility (i.e., reduced erlotinib solubility with increasing pH)	avoid concurrent use where possible: for antacids, suggest separate administration by several hours[19]; for twice daily ranitidine, take erlotinib at least 2 h before or 10 h after the ranitidine.[4]
grapefruit or grapefruit juice[1]	may increase plasma level of erlotinib	may inhibit CYP3A4 metabolism of erlotinib in the intestinal wall	avoid grapefruit and grapefruit juice
ketoconazole[1]	increases plasma levels of erlotinib	inhibits hepatic CYP3A4 metabolism of erlotinib	decrease dose of erlotinib if toxicity is observed; use caution with other CYP3A4 inhibitors
rifampin[1]	decreases plasma levels of erlotinib	induces hepatic CYP3A4 metabolism of erlotinib	clinical significance unclear; if possible, consider other treatments without CYP3A4 inducing activity
warfarin[1]	may increase INR and bleeding events	unknown	monitor INR and adjust warfarin dose as needed

Erlotinib is a major CYP3A4 substrate and therefore drugs that are CYP3A4 inhibitors (e.g., calcium channel blockers, azole antifungals, macrolide antibiotics, fluoroquinolone antibiotics, and some HIV antivirals) could potentially increase the pharmacological effects of erlotinib.[1] Drugs that induce CYP3A4 (e.g., barbiturates, anticonvulsants, glucocorticoids, St. John's Wort, and some HIV antivirals) could potentially decrease the pharmacological effects of erlotinib. Erlotinib is also a minor CYP1A2 substrate.

SUPPLY AND STORAGE:

Oral: Hoffmann-La Roche Limited supplies erlotinib as 25 mg, 100 mg or 150 mg film-coated tablets. Store at room temperature. Tablets contain lactose.[3]

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***

Oral:

150 mg PO once daily[1,20]
Take at least one hour before or two hours after the ingestion of food.[1]

When dose reduction is necessary, the dose should be reduced in 50 mg increments.[1]

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"

Dosage in renal failure: no information found

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

Dosage in hepatic failure:	In the setting of normal pretreatment values, interrupt or discontinue if total bilirubin is greater than 3 x Upper Limit of Normal and/or transaminases are greater than 5 x Upper Limit of Normal.[12] In the setting of pretreatment values outside of the normal range, interrupt or discontinue if total bilirubin doubles and/or transaminases triple.[12]
Dosage in elderly:	no adjustment required[1]
Dosage in dialysis:	no information found

Children:

Oral: safety and effectiveness in pediatric patients has not been studied[5]

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