

DRUG NAME: Lapatinib**SYNONYM(S):** lapatinib ditosylate monohydrate,¹ lapatinib tosylate,² GW572016³**COMMON TRADE NAME(S):** TYKERB®**CLASSIFICATION:** miscellaneous*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Lapatinib is an orally active small molecule tyrosine kinase inhibitor. It is a potent, reversible, and selective inhibitor of both EGFR and HER2 receptors, and induces growth arrest or apoptosis in EGFR-dependent or HER2-dependent tumour cell lines.^{1,4} Lapatinib binds to the intracellular cytoplasmic ATP-binding site of the tyrosine kinase domain, blocking receptor phosphorylation and activation, thereby blocking downstream signaling pathways.⁵

PHARMACOKINETICS:

Oral Absorption	incomplete and variable; increased when administered with food	
Distribution	highly protein bound; peak plasma concentrations in 4h	
	cross blood brain barrier?	yes ⁵
	volume of distribution	no information found
	plasma protein binding	>99% to albumin and alpha-1 acid glycoprotein
Metabolism	extensive; primarily by CYP 3A4 and CYP 3A5, minor metabolism by CYP 2C19 and CYP 2C8 to oxidized metabolites	
	active metabolite(s)	activity not characterized
	inactive metabolite(s)	activity not characterized
Excretion	primarily in feces; increased systemic exposure with moderate to severe hepatic impairment	
	urine	<2%
	feces	3-67% as unchanged drug and oxidized metabolites
	terminal half life	14 h after single dose, 24 h with repeated dosing ^{2,6}
	clearance	no information found
Ethnicity	incidence of dermatologic events may be higher in Hispanics (70%), as compared to white (63%), black (62%), Asians (58%), or others (65%); however, treatment interventions (dose modifications or treatment interruptions) appear to be similar between ethn racial subgroups ⁷	

Adapted from standard reference¹ unless specified otherwise.**USES:****Primary uses:**

*Breast cancer

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:**Caution:**

- lapatinib is associated with QT/QT_c prolongation. Patients who are at risk for developing torsades de pointes (an atypical ventricular tachycardia with changes in QT interval) include those with cardiac disease, history of arrhythmias, electrolyte disturbances, nutritional deficits, etc. and should be closely monitored. Baseline and periodic electrolyte measurements and electrocardiograms with QT measurement should be considered. Concurrent therapy with other QT prolonging drugs may increase the risk of potentially fatal arrhythmias and should be avoided if possible; see paragraph in **Interactions** section.¹
- concurrent medication should be carefully reviewed for potential drug interactions, particularly in regard to CYP 3A4, CYP 2C8, P-glycoprotein, BCRP and OATP1B1¹; see paragraphs in **Interactions** section.
- hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to treatment initiation. Caution is advised with concurrent medications that disrupt electrolyte levels, including diuretics, laxatives, and high dose corticosteroids.¹
- lapatinib has been reported to decrease left ventricular ejection fraction (LVEF). LVEF should be evaluated prior to initiation of therapy and periodically throughout treatment (eight week intervals have been used in clinical trials); see table and paragraph in **Side Effects** section.¹
- interstitial lung disease and pneumonitis have been associated with treatment. Patients should be monitored for pulmonary symptoms, and treatment discontinued if reported symptoms are Grade 3 or greater.¹
- hepatotoxicity has been observed. Liver function should be monitored prior to initiation of therapy, every four to six weeks during treatment, and as clinically indicated; see table and paragraph in **Side Effects** section.¹
- the presence of food significantly alters the bioavailability of lapatinib, with 3-5 fold increases in AUC reported with low and high fat meals relative to fasting. Multiple mechanisms are believed to be involved. Administration on an empty stomach is believed to be the most reliable way to achieve consistent systemic exposure and reduce potential toxicity during chronic therapy.^{1,8}

Carcinogenicity: No evidence of carcinogenicity in mammalian studies at doses up to twice the expected human clinical exposure.¹

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

Fertility: No effects on mammalian gonadal function, mating, or fertility at doses up to 3-8 times the expected human clinical exposure.¹

Pregnancy: FDA Pregnancy Category D.⁹ Lapatinib was not teratogenic in mammalian studies, but decreased pup survival, decreased fetal body weights, and minor skeletal anomalies in mammals have been reported.¹ 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

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.¹⁰⁻¹²

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
allergy/immunology	anaphylaxis (<1%)
blood/bone marrow/ febrile neutropenia	no information found

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
cardiovascular (arrhythmia)	QT/QT_c prolongation
cardiovascular (general)	LVEF reduction (1-3%) ^{5,13,14} ; see paragraph following Side Effects table
constitutional symptoms	fatigue (10-20%, severe <3%) ^{3,4}
dermatology/skin	dry skin ⁷ (3%); see paragraph following Side Effects table
	hair disorder ⁷ (3%)
	nail disorders, including paronychia (<1%) ⁷ ; see paragraph following Side Effects table
	pruritus/urticaria ^{7,14} (3-18%); see paragraph following Side Effects table
	rash (18-43%, severe 1-4%) ^{3,4,7} ; see paragraph following Side Effects table
	skin disorder, undefined ⁷ (1%)
gastrointestinal	<i>emetogenic potential</i> : low ¹⁵
	anorexia ⁴ (16%, severe <1%)
	diarrhea (36-59%, severe 3-10%) ^{3,4,14,16} ; see paragraph following Side Effects table
	nausea (10-20%, severe 1-2%) ^{3,4,14}
	vomiting ⁴ (13%, severe 2%)
hepatobiliary/pancreas	hepatotoxicity ^{1,14} (<1%); see paragraph following Side Effects table
infection	skin infection ⁷ (<1%)
metabolic/laboratory	ALT or AST > 3 times ULN (<1%)
	total bilirubin > 1.5 times ULN (<1%)
pain	back pain ⁴ (11%, severe 3%)
pulmonary	dyspnea ⁴ (14%, severe <5%)
	interstitial lung disease (<1%); discontinue if symptoms grade 3 or greater
	pneumonitis (<1%); discontinue if symptoms grade 3 or greater

Adapted from standard reference¹ unless specified otherwise.

Diarrhea is commonly reported, mainly as grade 1 or 2 events.¹⁴ Moderate to severe diarrhea may be complicated by severe cramping, nausea or vomiting, fever or dehydration.⁵ Diarrhea incidence appears to be related to dose, but not serum concentration, suggesting a local effect on the gut as opposed to a systemic effect.^{3,8} Proactive management with anti-diarrheal agents is important. A loperamide dosing regimen, including an initial dose of 4 mg, followed by 2 mg every four hours, and continued until twelve hours diarrhea-free, has been suggested. Therapy interruption or discontinuation may be required until recovery, and severe cases may also require oral or intravenous electrolytes and fluids.^{1,5}

Hepatotoxicity, although reported in less than 1%, may be severe and may occur days to several months after treatment initiation. ALT or AST greater than three times the upper limit of normal and total bilirubin of 1.5 times the upper limit of normal have been described. Deaths have been reported, although causality is uncertain. Monitor liver function tests (transaminases, bilirubin, and alkaline phosphatase) before treatment initiation, every four to six weeks during treatment, and as clinically indicated. Lapatinib should be discontinued and not restarted if liver function changes are severe or if severe hepatotoxicity develops during treatment, as moderate to severe hepatic impairment has been associated with 56-85% increases in systemic exposure. Clinical experience with severe pre-existing hepatic impairment is limited and safety and efficacy data are not available. Based on pharmacokinetic modeling, it has been suggested that a dose reduction from 1250 mg/day to 750 mg/day is warranted.¹

Left ventricular ejection fraction (LVEF) has been reported to decrease with lapatinib.¹ Events are usually reversible and asymptomatic.^{5,14,17} Caution is advised in patients with conditions that impair left ventricular function.¹ Previous anthracycline or trastuzumab treatment are suggested as possible risk factors for cardiotoxicity, although similar rates of occurrence have been reported for pretreated patients in pooled data.^{13,14,17} The majority of LVEF decreases (69%) occurred within the first 9 weeks of treatment during clinical trials, but long-term data is limited.^{1,13} Events resolved or improved in 62% of patients, with 42% of these continuing treatment. Average event duration was reported to be 4 weeks. Symptomatic events responded to standard CHF therapy in most.¹³ Baseline LVEF should be evaluated in all patients prior to initiation of treatment and periodically throughout treatment. LVEF was monitored at eight week intervals during clinical trials. Lapatinib should be discontinued in patients with symptoms associated with decreased LVEF (grade 3 or greater), or if LVEF drops 20% or greater relative to baseline or below the lower limit of normal.^{1,5} Treatment may be reconsidered with a dose reduction from 1250 mg/day to 1000 mg/day after a minimum of 2 weeks, but only if LVEF recovers to normal and the patient is asymptomatic.¹

Concentration dependent QT/QT_c interval prolongation has been reported with lapatinib. Events of ventricular fibrillation, cardiac arrest, and sudden death have been reported. Risk factors for experiencing torsade de pointes during treatment with a QT/QT_c prolonging drug include female gender, age ≥65 years, family history, history of cardiac disease or arrhythmias, electrolyte disturbances, acute neurological events, hepatic dysfunction, diabetes, and nutritional deficits. Concurrent therapy with other QT/QT_c prolonging drugs should be avoided where possible. Hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to lapatinib treatment.¹

Rash (including rash, acne, and dermatitis acneiform) is generally mild to moderate in intensity. Skin rash generally appears on the trunk, and sometimes the face.⁷ Rash incidence does not appear to relate to dose, serum concentration or clinical response to treatment.³ Onset of rash and **other dermatologic events** tends to develop early in treatment, usually occurring between days 2 to 66, with a median duration of 29 days. Most dermatologic events with lapatinib monotherapy resolve without dose adjustment or treatment interruption.^{3,7} Treatment should be permanently discontinued for intolerable grade 3 or 4 reactions or for grade 3 or 4 reactions which recur after treatment interruption and rechallenge.⁷ Patients are advised to moisturize dry skin with a thick alcohol-free emollient upon treatment initiation and minimize sun exposure for treatment duration. Appropriate use of sunscreen is recommended to prevent exacerbation of dermatologic toxicity. Treatment of dermatologic events is anecdotal and is based on type of reaction and severity of toxicity: skin rash may respond to short-term oral steroids; topical or systemic antihistamines may be beneficial for pruritic reactions; antiseptic baths, potent local corticosteroids, and silver nitrate are recommended to treat paronychia; and topical or systemic antibiotics are indicated for superinfection.^{5,7}

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit and grapefruit juice ¹	may increase plasma level of lapatinib	may inhibit CYP 3A4 metabolism of lapatinib in the intestinal wall	avoid grapefruit and grapefruit juice

Lapatinib is a weak base with low, pH dependent solubility that declines above pH 4.⁸ Clinical significance is unknown. It has been suggested that antacids which modify gastric pH may affect lapatinib absorption and should be avoided for 1 hour pre and post lapatinib doses.⁵

Lapatinib is a substrate for CYP 3A4. Strong inducers and inhibitors of this enzyme may alter lapatinib pharmacokinetics. Concurrent use with strong inducers or inhibitors should be avoided as clinical data for dose adjustment is lacking. Based on pharmacokinetic studies, however, it is suggested that if co-administered with a strong CYP 3A4 inhibitor, lapatinib dose reduction from 1250 mg/day to 500 mg/day could be considered, with a washout period of 1 week if the inhibitor is discontinued, or if co-administered with a strong CYP 3A4 inducer, gradual titration of lapatinib to 1250-4500 mg/day (based on tolerability), with gradual dose reduction over 2 weeks if the inducer is discontinued.¹

Lapatinib is an inhibitor of CYP 3A4, therefore, it may decrease the metabolism or increase bioavailability of substrates of this enzyme. Concurrent therapy is discouraged. Dose reduction of the substrate drug should be considered.¹

Lapatinib inhibits CYP 2C8 *in vitro* and may decrease the metabolism of substrates of this enzyme. Dose reduction of the substrate drug should be considered.¹

Lapatinib is a substrate for the transport proteins P-glycoprotein and BCRP. Inhibitors or inducers of these proteins may alter the exposure or distribution of lapatinib and QT prolongation is expected to be increased in the presence of inhibitors of these proteins. [Drugs that prolong QT/QT_c interval should be avoided due to the risk of potentially fatal arrhythmias.](#)¹

In vitro, lapatinib is an inhibitor of the transport proteins P-glycoprotein, BCRP, and OATP1B1. Clinical relevance of this effect has not been established but elevated bilirubin may occur due to inhibition of hepatic uptake or reduced excretion into bile. Reduced metabolism of substrates of these proteins is considered likely, resulting in increased concentrations of the substrate drugs.¹

SUPPLY AND STORAGE:

Oral: GlaxoSmithKline Inc. supplies lapatinib ditosylate as 250 mg film-coated tablets. Store at room temperature.¹

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:

<i>Oral:</i>	1250 mg PO once daily Administer on an empty stomach (one hour before or one hour after meals). Do not take with food. ^{1,8}
<i>Concurrent radiation:</i>	has been used ¹⁸
<i>Dosage in myelosuppression:</i>	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"
<i>Dosage in renal failure:</i>	dosage adjustment likely not required; less than 2% eliminated by kidneys ¹
<i>Dosage in hepatic failure:</i>	moderate and severe impairment have been associated with increased systemic exposure; consider dose reduction to 750 mg PO once daily; treatment should be stopped if severe hepatotoxicity develops ¹
<i>Dosage in dialysis:</i>	no information found ¹

Children: no information found

REFERENCES:

1. GlaxoSmithKline Inc. TYKERB® product monograph. Mississauga, Ontario; 14 May 2009.
2. MARTINDALE - The Complete Drug Reference (database on the Internet). Lapatinib tosilate. Thomson MICROMEDEX®, 2008. Available at: <http://www.micromedex.com/>. Accessed 10 September 2009.
3. Burris III HA, Hurwitz HI, Dees EC, et al. Phase I safety, pharmacokinetics, and clinical activity study of lapatinib (GW572016), a reversible dual inhibitor of epidermal growth factor receptor tyrosine kinases, in heavily pretreated patients with metastatic carcinomas. *J Clin Oncol* 2005;23(23):5305-5313.
4. Kaufman B, Trudeau M, Awada A, et al. Lapatinib monotherapy in patients with HER2-overexpressing relapsed or refractory inflammatory breast cancer: final results and survival of the expanded HER2+ cohort in EGF103009, a phase II study. *Lancet Oncol* 2009;10(6):581-588.
5. Moy B, Goss PE. Lapatinib-associated toxicity and practical management recommendations. *Oncologist* 2007;12:756-765.

6. DRUGPOINT® Summary (database on the Internet). Lapatinib. Thomson MICROMEDEX®, 2009. Available at: www.micromedex.com. Accessed 10 Sept 2009.
7. Lacouture ME, Laabs SM, Koehler M, et al. Analysis of dermatologic events in patients with cancer treated with lapatinib. *Breast Cancer Res Treat* 2009;114:485-493.
8. Koch KM, Reddy NJ, Cohen RB, et al. Effects of food on the relative bioavailability of lapatinib in cancer patients. *J Clin Oncol* 2009;27(8):1191-1196.
9. Rose BD editor. Lapatinib. UpToDate 17.2 ed. Waltham, Massachusetts: UpToDate®; 2009.
10. Caroline Lohrisch MD. Personal communication. BC Cancer Agency Breast Tumour Group; 5 November 2009.
11. Kimberly Kuik RPh. Personal communication. BC Cancer Agency Breast Tumour Group; 06 November 2009.
12. Kimberly Kuik RPh. Personal communication. BC Cancer Agency Breast Tumour Group; 30 October 2009.
13. Perez EA, Byrne JA, Hammond IW, et al. Cardiac safety experience in 3127 patients treated with lapatinib. *Ann Oncol* 2006;17(suppl 9):ix69.
14. Gomez HL, Doval DC, Chavez MA, et al. Efficacy and safety of lapatinib as first-line therapy for ErbB2-amplified locally advanced or metastatic breast cancer. *J Clin Oncol* 2008;26(18):2999-3005.
15. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 March 2008.
16. McEvoy GK, editor. AHFS 2008 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc. p. 1130-1132.
17. Perez EA, Koehler M, Byrne J, et al. Cardiac safety of lapatinib: pooled analysis of 3689 patients enrolled in clinical trials. *Mayo Clin Proc* 2008;83(6):679-686.
18. Harrington KJ, El-Hariry IA, Holford CS, et al. Phase I study of lapatinib in combination with chemoradiation in patients with locally advanced squamous cell carcinoma of the head and neck. *J Clin Oncol* 2009;27(7):1100-1107.