Drug Monograph

A - Drug Name

lapatinib

COMMON TRADE NAME(S): Tykerb®

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B - Mechanism of Action and Pharmacokinetics

Lapatinib is a reversible, selective inhibitor of the intracellular tyrosine kinase domains of the Epidermal Growth Factor Receptor (EGFR/ErbB1), and Human Epidermal Receptor Type 2 (HER2/ErbB2).

Absorption	Oral Absorption: incomplete and variable. Divided daily doses result in a 2-fold higher exposure at steady state compared to once daily.	
	Effects with food	Food increases systemic exposure to lapatinib (approx. 3-4 fold higher AUC).
	Peak plasma levels	~ 4 hours
	Time to reach steady state	6 to 7 days
Distribution	Cross blood brain barrier?	Yes
	PPB	> 99% to albumin and α1-glycoprotein
Metabolism	Extensive metabolism by CYP3A4 and CYP3A5, and minor role from CYP2C19 and CYP2C8 to oxidated metabolites	
	Inactive metabolites	Yes

Elimination	Feces	27% (range 3 - 67%)
	Urine	Less than 2%
	Half-life	24 hours

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C - Indications and Status

Health Canada Approvals:

- Breast cancer

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

The following table contains adverse effects reported in ≥ 10% of patients in a phase I trial, with HR + advanced or metastatic breast cancer, receiving the combination with letrozole, where incidences were higher than letrozole alone. Rare or severe adverse effects from other trials are also included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Cardiotoxicity (3%)	E D
	QT interval prolonged (rare)	E
Dermatological	Alopecia (13%)	E
	Erythema multiforme (rare)	E
	Nail disorder (11%)	E
	Rash, pruritus (44%) (1% severe) (including dry skin)	E
	Stevens-Johnson syndrome (rare)	E
	Toxic epidermal necrolysis (rare)	E
Gastrointestinal	Anorexia (11%)	E
	Diarrhea (64%) (9% severe)	E

	Nausea, vomiting (31%)	E
General	Fatigue (20%)	E
Hepatobiliary	↑ LFTs (6%) (severe)	E
Hypersensitivity	Hypersensitivity (rare)	I
Nervous System	Headache (14%)	E
Respiratory	Epistaxis (11%)	E
	Pneumonitis (rare)	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 common side effects when lapatinib is used in combination with letrozole include diarrhea, rash/pruritus, nausea, vomiting, fatigue, headache, alopecia, anorexia, epistaxis and nail disorder.

Rare but serious **cardiotoxic events,** including congestive heart failure, have been reported. Decreases in **left ventricular ejection fraction** have been reported with a majority of cases occurring within the first 12 weeks of treatment. Long term data are not available. Concentration dependent increases in QTc with Torsades de Pointes, ventricular fibrillation, cardiac arrest and sudden death have been reported.

Severe **hepatotoxicity**, including fatal cases, has occurred in clinical trials within days to several months after treatment initiation.

Diarrhea is common and should be proactively managed at the first sign of symptoms and re-assessed after 24 hours. Symptoms with lapatinib treatment are generally low-grade, occur early (< 1 week of starting treatment) and last 4-5 days. If patients experience Grade 1 or 2 diarrhea, maintain hydration, give frequent small meals and administer antidiarrheals such as loperamide. In severe cases, or accompanied by severe cramping, severe nausea or vomiting, fever or dehydration, hold or discontinue lapatinib; administration of oral or IV hydration and electrolytes and or antibiotics may be required (See Dosing section).

Rash is common and has been seen as a class effect of EGFR inhibitors. It is characterized by inflammatory papules and pustules, and most often seen on the face, chest and back. Oral antibiotics such as minocycline 100mg PO bid and colloidal oatmeal lotion have been shown to be effective. Emollients may be useful for the dry skin component of this rash. Patients should avoid sun exposure and use sunscreen with an SPF ≥ 30 as lapatinib increases the risk of photosensitivity.

Severe **skin reactions**, including Stevens-Johnson syndrome, toxic epidermal necrolysis and skin fissures have been reported post-marketing.

In monotherapy and combination chemotherapy trials, lapatinib has been associated with **interstitial lung disease** and **pneumonitis**.

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E - Dosing

Refer to protocol by which the patient is being treated.

Use only with HER-2 overexpression, confirmed by validated test. Refer to the product monograph for details.

Correct electrolyte abnormalities (hypokalemia, hypocalcemia or hypomagnesemia) prior to treatment.

Patients should be provided with information on how to manage diarrhea, including provision of loperamide (Imodium®) for early treatment.

Patients should avoid sun exposure and use sunscreens with SPF ≥ 30.

Adults:

With capecitabine:

Oral: 1250mg Daily

For capecitabine dosing refer to CAPELAPA RM.

Dosage with Toxicity:

Refer to **Interactions section** for dosing recommendations when co-administered with CYP3A4 inhibitors.

Dose Level	Lapatinib Dose (mg/day)
0	1250
-1	1000
-2	750
-3	Discontinue

Toxicity	Grade	Action*
Hematologic	Grade 2	Hold until recovery and then restart at the same dose.
	≥ Grade 3	Hold until recovery and then ↓ 1 dose level.
LVEF impairment	≥ 20% decrease from baseline, or lower than institution's LLN, or ≥ Grade 3	Discontinue and monitor patient closely. If after 2 weeks LVEF ≥ normal and patient asymptomatic, resume at ↓ 1 dose level. Monitor closely. If recurs, discontinue.
Pneumonitis/interstitial lung disease	Any	Hold and investigate; discontinue if ≥ Grade 3 confirmed.
Severe changes in liver function	Any	Discontinue
Severe skin reactions (i.e. SJS, TEN, erythema multiforme)	Any	
Diarrhea	Grade 1-2 without complicating factors**	Start loperamide. If no improvement, hold until resolution, then restart. If recurs, ↓ 1 dose level.
	Grade 1-2 with complicating factors** or Grade 3	Hold until ≤ grade 1; treat with loperamide. Consider IV electrolytes/hydration and antibiotics if appropriate. When resolved to ≤ grade 1 restart at ↓ 1 dose level.
	Grade 4	Discontinue
All other non-hematological	Grade 2-3	Hold until resolved to ≤ grade 1. Restart at same dose level If the toxicity recurs, hold until resolved to ≤ grade 1. Restart at ↓ 1 dose level.
	Grade 4	Hold until resolved to ≤ grade 1. Restart at ↓ 1 dose level. Consider discontinuing if clinically appropriate.

*Before re-treatment, major organ toxicities must recover to ≤ grade 1 within 14 days of treatment interruption; otherwise, discontinue.

** Complicating factors include ↓ performance status, fever, sepsis, neutropenia, frank bleeding, dehydration, moderate to severe cramping or nausea/vomiting

Dosage with Hepatic Impairment:

Lapatinib is metabolized in the liver. Moderate and severe hepatic impairment have been associated with 56% and 85% increases in systemic exposure, respectively.

Pre-existing Hepatic Impairment	Lapatinib Starting Dose
Mild or Moderate (Child-Pugh class A or B)	No dosage adjustment required. Use with caution.
Severe (Child-Pugh class C)	No clinical data; use extreme caution. May consider starting at ↓ 2 dose levels*

*Starting dose of 750 mg/day in combination with capecitabine

Dosage with Renal Impairment:

No information found. Renal impairment is unlikely to affect lapatinib pharmacokinetics, since renal elimination accounts for less than 2% of the excreted dose.

Dosage in the elderly:

No dosage adjustment required. Limited data available. Patients ≥ 65 years appear to have higher incidence of edema and an earlier onset of cardiac toxicity.

Children:

Safety and efficacy of lapatinib have not been established.

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F - Administration Guidelines

- Take once daily; do not give in divided daily doses
- Take on an empty stomach, at least 1 hour before, or at least 1 hour after a low-fat meal.
- Avoid grapefruit, starfruit, Seville oranges and their juices/products while on lapatinib treatment.
- Missed doses should not be replaced; dosing should resume with the next scheduled daily dose.

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G - Special Precautions

Contraindications:

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

Other Warnings/Precautions:

- Exercise caution in patients with HER2 negative status given the lack of benefit in this group
- Patients with conditions that can impair left ventricular function, or in patients at risk of experiencing QT prolongation or Torsades de Pointes (females, age 65 or older, baseline QT prolongation, cardiac disease, history of arrhythmias, electrolyte disturbances, bradycardia, diabetes, concurrent drugs that prolong QT interval, etc)
- Exercise caution in patients with severe pre-existing hepatic impairment as they were excluded from clinical trials
- Exercise caution in patients with HLA alleles DQA1*02:01 and DRB1*07:01 as they are associated with increased risk of lapatinib associated hepatotoxicity.

Other Drug Properties:

- Carcinogenicity: No

Pregnancy and Lactation:

- Clastogenicity: No
- Mutagenicity: No
- Teratogenicity: No
- Fetotoxicity: Yes
  Lapatinib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **5 days** after the last dose (for females).
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended during treatment and for at least **5 days** after the last dose.
- Fertility effects: Unknown

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H - Interactions

Extensive metabolism by CYP3A4 and CYP3A5, and minor role from CYP2C19 and CYP2C8 to oxidated metabolites.

Lapatinib inhibits CYP3A4 and CYP2C8 and the transport proteins P-glycoprotein , BCRP and OATP1B1. Lapatinib is a substrate for the transport proteins P-glycoprotein and BCRP.

Co-administration of lapatinib with capecitabine or letrozole did not significantly affect the pharmacokinetics of either drug, or of lapatinib itself.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ lapatinib exposure, toxicity; increased risk of QT prolongation.	↓ lapatinib metabolism (3.6x ↑ in AUC with ketoconazole)	Avoid concomitant use of strong inhibitors. If concomitant use cannot be avoided, ↓ lapatinib to 500mg/day. Do not ↑ until after a 1-week washout period. Caution with use of moderate CYP3A4 inhibitors and monitor for toxicity.
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine,	↓ lapatinib plasma concentration and decreased efficacy	↑ lapatinib metabolism (↓ exposure ~ 72% with carbamazepine)	Avoid concomitant use of strong inducers. If concomitant use cannot be avoided, ↑ dose of lapatinib

phenobarbital, St. John's Wort, etc)			based on tolerability. Decrease dose if inducer is discontinued gradually over approximately 2 weeks.
Drugs that may prolong QT (i.e. Amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)	↑ risk of QT prolongation and/or torsade de pointes	Additive	Avoid concomitant use
CYP3A4 substrates (e.g. midazolam, cyclosporine, pimozide, tacrolimus, triazolo-benzodiazepines, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors)	↑ substrate drug concentration and toxicity	Lapatinib is an inhibitor of CYP3A4 (↑ AUC of oral midazolam by 45%)	Caution, especially for substrates with narrow therapeutic index. Consider dose reduction of the concomitant substrate drug.
CYP 2C8 substrates (i.e. paclitaxel, sorafenib, amiodarone)	↑ substrate drug concentration and toxicity.	Lapatinib is an inhibitor of CYP2C8	Caution, especially for substrates with narrow therapeutic index.
Substrates of P-glycoprotein, BCRP, OATP1B1 (i.e. digoxin, topotecan,	Elevated bilirubin; ↑ substrate drug concentration	Lapatinib inhibits P-gp and hepatic drug uptake by OATP1B1 (↑ AUC by 98% with digoxin). Lapatinib	Caution, especially for substrates with narrow therapeutic index.

rosuvastatin)		inhibits drug excretion into bile by Pgp or BCRP	
Drugs that disrupt electrolyte levels (i.e. loop/thiazide diuretics, laxatives, amphotericin B, high dose corticosteroids)	↑ risk of arrhythmia / QT prolongation.	Electrolyte imbalances	Caution
Inhibitors of P-glycoprotein and BCRP (i.e. quinidine, cyclosporine)	↑ toxicity; increased risk of QT prolongation.	↑ lapatinib exposure	Caution
Inducers of P-glycoprotein and BCRP (i.e. rifampin, dexamethasone)	↓ lapatinib efficacy	↓ lapatinib exposure	Caution
Proton pump inhibitors	↓ lapatinib efficacy	↓ lapatinib exposure (27% with esomeprazole)	Caution

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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
Liver function tests	Baseline, every 4 to 6 weeks during treatment, and as clinically indicated
Electrolytes	Baseline and at each visit
LVEF evaluation	Baseline and as clinically indicated
CBC	Baseline and as clinically indicated
Renal function tests	Baseline and as clinically indicated

Skin examination	Before treatment and at each visit during treatment. If a skin reaction occurs, a full body examination should be performed at every visit until one month after resolution
Clinical assessment for GI, cardiac and pulmonary toxicities	Baseline and as clinically indicated

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
ECG, for patients at risk of developing QT prolongation.	Baseline and as clinically indicated

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- lapatinib - Second-Line treatment of HER2 positive metastatic breast cancer in combination with chemotherapy after previous exposure to trastuzumab based treatments, with specific criteria
- lapatinib - Treatment of HER-2 positive metastatic breast cancer when used in combination with chemotherapy after use of trastuzumab in patients who have an adverse drug reaction or contraindication to trastuzumab therapy

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K - References

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letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. J Clin Oncol 2009;27(33):5538-46.

Lin NU, Carey LA, Liu MC, et al. Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol. 2008 Apr 20;26(12):1993-9.

Moy B and Goss PE. Lapatinib-associated toxicity and practical management recommendations. The Oncologist 2007; 12: 756-65. Prescribing Information: Tykerb® (lapatinib). Novartis Pharmaceuticals Corporation. February 2021.

Prescribing Information: Tykerb® (lapatinib). Novartis Pharmaceuticals Corporation. February 2021.

Product monograph: Tykerb® (lapatinib), GlaxoSmithKline Inc. (Canada), December 2018.

June 2022 Updated Dosing and Recommended Clinical Monitoring 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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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare

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