Regimen Monograph

A - Regimen Name

CAPELAPA Regimen

Capecitabine-Lapatinib

Disease Site	Breast
Intent	Palliative
Regimen Category	**Evidence-Informed :** Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.
Rationale and Uses	For second-line treatment of HER2-positive metastatic breast cancer after previous exposure to trastuzumab-based treatments. Usage is also funded for patients in whom further trastuzumab is contraindicated / not tolerated. Note: The phase III clinical trial included only patients with good performance status.

Supplementary Public Funding

capecitabine
ODB - General Benefit (capecitabine)

lapatinib
Exceptional Access Program (lapatinib - Second-Line treatment of HER2 positive metastatic breast cancer in combination with chemotherapy after previous exposure to trastuzumab based treatments, with specific criteria) (EAP Website)

lapatinib
Exceptional Access Program (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) (EAP Website)

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B - Drug Regimen

capecitabine	1000 mg /m²	PO	BID* Days 1 to 14

* Total dose 2000mg/m^2/day

AND

lapatinib	1250 mg	PO	Once daily Days 1 to 21

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Until evidence of disease progression, or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low – No routine prophylaxis; PRN recommended

Other Supportive Care:

- Patients should be provided with information on how to manage diarrhea, including provision of loperamide (Imodium®) for early treatment.
- Topical emollients (e.g. hand creams, udder balm) may ameliorate the manifestations of hand-foot syndrome in patients receiving capecitabine.
- For lapatinib-induced rash, colloidal oatmeal lotion and oral antibiotics such as minocycline 100mg PO BID have been shown to be effective. Emollients may be useful for the dry skin component of this rash.
- Patients should be advised to avoid sun exposure and use sunscreen with SPF ≥ 30.

Also refer to CCO Antiemetic Recommendations.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Patients should be tested for DPD deficiency before starting treatment with capecitabine. Refer to the DPD Deficiency Guidance for Clinicians for more information.

In patients with unrecognized DPD deficiency, acute, life-threatening toxicity may occur; if acute grade 2-4 toxicity develops, treatment should be stopped immediately and permanent discontinuation considered based on clinical assessment of the toxicities.

Electrolyte abnormalities (hypokalemia, hypocalcemia or hypomagnesemia) should be corrected before starting treatment.

Dosage with toxicity

Dose Modifications for Lapatinib

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	≥ 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 Adjustments for Capecitabine

Do not start treatment with capecitabine unless baseline neutrophil counts are ≥ 1.5 x 10^9/L and/or platelet counts of ≥ 100 x 10^9/L.

Patients should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs.

Doses should not be re-escalated if reduced for toxicity. Missed or omitted doses of capecitabine should not be replaced.

Capecitabine dose modifications are mandatory for gastrointestinal, dermatological toxicity and hyperbilirubinemia. Practitioner may elect not to reduce dose for other toxicities unlikely to become serious or life-threatening.

Non-hematologic Toxicity:

Toxicity	Action During a Course of Therapy	Dose Adjustment for Next Cycle (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2 1st appearance 2nd appearance 3rd appearance 4th appearance	 Hold until resolved to ≤ grade 1 Hold until resolved to ≤ grade 1 Hold until resolved to ≤ grade 1 Discontinue treatment permanently	 100% 75% 50% Not applicable
Grade 3 1st appearance 2nd appearance 3rd appearance OR any evidence of Stevens-Johnson syndrome or Toxic Epidermal Necrolysis	 Hold until resolved to ≤ grade 1 Hold until resolved to ≤ grade 1 Discontinue treatment permanently	 75% 50% Not applicable
Grade 4 1st appearance, including SJS, TEN, OR cardiotoxicity, OR acute renal failure 2nd appearance	 Discontinue permanently OR If physician deems it to be in the patient's best interest to continue and no evidence of Stevens-Johnson syndrome or toxic epidermal necrolysis, interrupt until resolved to ≤ grade 1. Discontinue permanently	 Discontinue OR 50% Not applicable

Hematologic Toxicity:

Hold capecitabine during a treatment cycle in the presence of grade 3 or 4 hematologic toxicity.

Hepatic Impairment

Hepatic impairment	Capecitabine Starting Dose	Lapatinib Starting Dose
Mild to moderate (Child-Pugh class A or B)	No dosage adjustments required	No dosage adjustment required
Severe (Child-Pugh class C)	No data – do not use or use with extreme caution	No clinical data; use extreme caution; may consider starting at ↓ 2 dose levels. (i.e. 750 mg /day)

Renal Impairment

Creatinine Clearance (mL/min)	Capecitabine Dose (% previous dose)	Lapatinib Dose
51-80	100% (with close monitoring)	No dose adjustment required.
30-50	75%	
< 30	DISCONTINUE	

Dosage in the Elderly

No dose adjustment of the starting dose is required for capecitabine or lapatinib.

Patients should be closely monitored and dose modification should be performed as described above. Older patients are more susceptible to the effects of fluoropyrimidine-based therapies with increased grade 3 / 4 adverse effects, especially when used in combination. Patients ≥ 65 years appear to have higher incidence of edema and an earlier onset of cardiac toxicity with lapatinib.

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F - Adverse Effects

Refer to capecitabine, lapatinib drug monograph(s) for additional details of adverse effects

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Diarrhea (may be severe) • Hand-foot syndrome (may be severe)	• Rash (may be severe) • Nausea, vomiting	• Mucositis • Fatigue • ↑ Bilirubin • Headache • Alopecia • Anorexia • Nail disorder • Epistaxis • Abdominal pain	• Myelosuppression +/- infection, bleeding • Cardiotoxicity • Prolonged QT interval • Arterial/venous thromboembolism • GI obstruction/perforation • Hepatic failure • Pneumonitis • Hypersensitivity • Stevens Johnson syndrome • Toxic epidermal necrolysis • Erythema multiforme • Leukoencephalopathy • Eye disorders • Nephrotoxicity • ITP

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G - Interactions

Refer to capecitabine, lapatinib drug monograph(s) for additional details

- Avoid concomitant use of lapatinib with strong CYP3A4 inhibitors, due to ↑ lapatinib levels. If concomitant used cannot be avoided, ↓ lapatinib to 500 mg/day. Do not ↑ until after a 1-week washout period.
- Avoid concomitant use of lapatinib with CYP3A4 inducers, due to ↓ lapatinib levels. If concomitant use cannot be avoided, ↑ dose of lapatinib based on tolerability. Decrease dose if inducer is discontinued gradually over approximately 2 weeks.
- Consider dose reduction of CYP3A4 substrates when used concomitantly with lapatinib, especially those with narrow therapeutic indices; concomitant use may ↑ substrate drug concentration and toxicity.
- Avoid concomitant use of lapatinib with drugs that prolong the QT interval, due to ↑ risk of QT prolongation and/or torsade de pointes.
- Concomitant use of capecitabine with sorivudine and related analogues is contraindicated, as these increase capecitabine toxicity (may be fatal). Wait at least 4 weeks after sorivudine (or chemically related analogues) treatment before starting capecitabine.
- Avoid concomitant administration of capecitabine with phenytoin/fosphenytoin as capecitabine may ↑ levels of phenytoin. Monitor phenytoin/fosphenytoin levels if used together.
- Caution and monitor PT/INR when capecitabine administered with warfarin, as capecitabine increases warfarin exposure.
- Caution with the use of proton pump inhibitors and monitor for reduced effectiveness of capecitabine; consider switching to a magnesium and aluminum hydroxide-containing antacid.

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H - Drug Administration and Special Precautions

Refer to capecitabine, lapatinib drug monograph(s) for additional details

Administration

Capecitabine:

- Oral self-administration; drug available by outpatient prescription.
- Doses are given orally approximately 12 hours apart, within 30 minutes after the end of a meal.
- Swallow tablets whole; do not crush or cut tablets.
- If a capecitabine dose is missed, skip this and give the next dose at the usual time. Missed or omitted doses should not be replaced.
- Store tablets at 15ºC to 30ºC in the original package.

Lapatinib:

- 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.

Contraindications

- Patients who have a known hypersensitivity to lapatinib, capecitabine, their excipients, or 5-fluorouracil
- Patients with severe renal impairment (CrCl <30 mL/min), with capecitabine
- Patients with known near or complete absence of DPD (dihydropyrimidine dehydrogenase) activity, with capecitabine. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- Concomitant use with sorivudine or related analogues (i.e. brivudine), given potential fatal drug interaction (see drug interactions), with capecitabine

Other Warnings / Precautions:

- Capecitabine contains lactose and should not be used in patients with hereditary galactose/glucose/lactase disorders.
- Use capecitabine with caution in patients with risk factors for dehydration, pre-existing renal dysfunction or on nephrotoxic agents.
- Use capecitabine with extreme caution in patients with partial DPD deficiency. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- Use with caution in patients with a history of cardiovascular disease.
- Use lapatinib with caution in 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
- 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*07:01as they are associated with increased risk of lapatinib associated hepatotoxicity.

Pregnancy / Lactation:

- This regimen is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **6 months** after the last dose.
- Breastfeeding is not recommended during treatment and for **2 weeks** after the last dose.
- Fertility effects:
    - Capecitabine: Probable
    - Lapatinib: Unknown

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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

- CBC; Baseline and at each visit
- Electrolytes; Baseline and at each visit
- Liver function tests; Baseline, every 4 to 6 weeks during treatment, and as clinically indicated
- Renal function tests; Baseline and at each visit
- LVEF evaluation; Baseline and as clinically indicated
- INR and/or PT; Baseline and as clinically indicated if patient is on anticoagulants
- 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, dehydration, infection, stomatitis, neurotoxicity and pulmonary toxicities; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- ECG for patients at risk of developing QT prolongation; Baseline and as clinically indicated

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J - Administrative Information

Outpatient prescription for home administration

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K - References

Cameron D, Casey M, Press M, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat 2008: 112: 533-43.

Capecitabine and lapatinib drug monographs, Ontario Health (Cancer Care Ontario).

Capri G, Chang J, Chen SC, et al. An open-label expanded access study of lapatinib and capecitabine in patients with HER2-overexpressing locally advanced or metastatic breast cancer. Ann Oncol 2010;21(3):474-80.

Geyer CE, Forster J, Lindquist D, et al. Lapatinib and capecitabine for HER2-positive advanced breast cancer. NEJM 2006; 355: 2733-43.

April 2023 Updated DPD deficiency information in the Dose Modifications and Special Precautions sections

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

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Regimen Monographs

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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