# Lapatinib and Capecitabine (breast)

## Indication

Advanced HER2+ breast cancer in patients who have received previous treatment with trastuzumab, anthracyclines and taxane containing therapies (unless contraindicated).

(Funding via CDF)

## ICD-10 codes

Codes with a prefix C50

## Regimen details

| Day | Drug | Dose | Route |
|---|---|---|---|
| 1-14* | Capecitabine | 1000mg/$m^2$ BD | PO |
| 1-21 | Lapatinib | 1250mg OD (continuously) | PO |

* For 14 days followed by a 7 day break

## Cycle frequency

21 days

## Number of cycles

Until disease progression or intolerable toxicity.

## Administration

Capecitabine is available as 150mg and 500mg tablets.

Tablets should be taken after food, swallowed whole with a glass of water.

Doses should be prescribed as per the following table:

| **Body surface area** ($m^2$) | **Capecitabine dose** (1000mg/$m^2$) |
|---|---|
| 1.23-1.39 | 1300mg BD |
| 1.40-1.57 | 1500mg BD |
| 1.58-1.72 | 1650mg BD |
| 1.73-1.89 | 1800mg BD |
| 1.90-2.07 | 2000mg BD |
| 2.08-2.22 | 2150mg BD |
| 2.23-2.39 | 2300mg BD |
| 2.40-2.57 | 2500mg BD |

For BSA < 1.23 or > 2.57 refer to consultant.

Lapatinib is available as 250mg tablets which should be taken as a single dose (not divided) either at least one hour before or after food, at the same time each day.

Grapefruit and grapefruit juice should be avoided while taking lapatinib.

Missed doses of capecitabine or lapatinib should not be replaced.

## Pre-medication
Nil

## Emetogenicity
This regimen has moderate-low emetic potential

## Additional supportive medication
Loperamide if required.
Topical emollients to prevent palmar plantar erythema
$H_2$ antagonist or proton pump inhibitor if required.
Mouthwashes as per local policy

## Extravasation
N/A

## Investigations – pre first cycle

| **Investigation** | **Validity period** (or as per local policy) |
|---|---|
| FBC | 14 days |
| U+E (including creatinine) | 14 days |
| LFTs | 14 days |
| ECHO/MUGA | 28 days |
| ECG | If clinically indicated |

## Investigations - pre subsequent cycles

| **Investigation** | **Validity period** (or as per local policy) |
|---|---|
| FBC | 96 hours |
| U+E (including creatinine) | 7 days |
| LFTs | 7 days |
| ECHO/MUGA | After 3 months and then 6 monthly (or as clinically indicated) |
| ECG | If clinically indicated |

## Standard limits for administration to go ahead
If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

| **Investigation** | **Limit** |
|---|---|
| Neutrophils | ≥ 1.0 x $10^9$/L |
| Platelets | ≥ 100 x $10^9$/L |
| Creatinine clearance (CrCl) | > 50 mL/min |
| Bilirubin | ≤ 3 x ULN |
| AST/ALT | ≤ 2.5 x ULN |

## Dose modifications
- **Haematological toxicity**

If neutrophils <1.0 x $10^9$/L and/or platelets <100 x $10^9$/L delay 1 week or until recovery.
If neutropenia results in a delay of > 1 week, reduce capecitabine to 75% dose and lapatinib to 1000mg.

- **Renal impairment**

| **CrCl (mL/min)** | **Capecitabine dose** | **Lapatinib dose** |
|---|---|---|
| >50 | 100% | 100% |
| 30-50 | 75% (with close monitoring) | 100% |
| <30 | Contra-indicated | Use with caution |

- **Hepatic impairment**

| **AST/ALT** (x ULN) | | **Bilirubin** (x ULN) | **Capecitabine dose** | **Lapatinib dose** |
|---|---|---|---|---|
| ≤ 2.5 | and | ≤ 3 | 100% | 100% |
| > 2.5 | or | > 3 | Consultant decision* | Caution (increased risk of toxicity) – consultant decision |

*current evidence does NOT suggest dose modification is necessary

- **Other toxicities**

**Capecitabine**:
Other toxicities should be managed by symptomatic treatment and/or dose modification (i.e. by treatment interruption or undertaking a dose reduction).
Once the dose has been reduced, it should not be increased at a later time.

For those toxicities considered unlikely to become serious or life-threatening (e.g. alopecia, altered taste or nail changes) treatment can be continued at the same dose without reduction or interruption.

Patients should be informed of the need to interrupt treatment immediately if they develop moderate or severe side effects particularly diarrhoea – not controlled by loperamide, palmar-plantar erythema or infection.

Capecitabine dose modifications should be made as per the following table:

| **Toxicity grade** | **1st occurrence** | **2nd occurrence** | **3rd occurrence** | **4th occurrence** |
|---|---|---|---|---|
| 0-1 | 100% | 100% | 100% | 100% |
| 2 | Delay then 100% | Delay then 75% | Delay then 50% | Discontinue |
| 3 | Delay then 75% | Delay then 50% | Discontinue | |
| 4 | Delay then 50% | Discontinue | | |

Any delays should be until the toxicity has resolved to grade 0-1.

**Lapatinib:**
Pneumonitis/interstitial lung disease – all patients should be monitored for symptoms of pulmonary toxicity. If ≤ grade 2 toxicity occurs withhold lapatinib and investigate the cause. If ≥ grade 3 toxicity occurs discontinue lapatinib.
If LVEF drops below the lower limit of normal (or ≥ grade 3 toxicity), withhold lapatinib for at least 2 weeks and reassess. If asymptomatic resume at 1000mg dose.

## Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Cardiotoxicity
Myelosuppression
Interstitial lung disease
Diarrhoea
Thrombus/embolism
Severe toxicity due to DPD deficiency (see comments below)

- **Frequently occurring side effects**

Nausea and vomiting
Stomatitis/Mucositis
Myelosuppression
Palmar plantar erythema
Fatigue
Skin reactions
Nail changes
Taste disturbance

- **Other side effects**

Myalgia
Fluid retention
Alopecia
Rash
Deranged liver function

## Significant drug interactions – for full details consult product literature/ reference texts

**Capecitabine:**
**Folinates:** Avoid concomitant use of folinic and folic acid – enhanced toxicity of fluorouracil.
**Co-trimoxazole/trimethoprim**: Avoid if possible – enhances antifolate effect. If essential, monitor FBC regularly.
**Warfarin/coumarin anticoagulants:** Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.
**Sorivudine, Allopurinol, Phenytoin**: close monitoring is necessary if prescribed with any of these agents.
**Antacids**: Aluminium hydroxide and magnesium hydroxide containing antacids have been shown to produce a slight increase in plasma concentration of capecitabine.

**Lapatinib:**
**CYP3A4 inducers** (e.g. carbamazepine, phenytoin, rifampicin, Phenobarbital, St. John's Wort): avoid or use with caution as these drugs reduce the bioavailability of lapatinib.
**CYP3A4 inhibitors** (e.g. ketoconazole, itraconazole, clarithromycin, nefazodone, saquinavir, telithromycin, ritonavir, voriconazole): avoid or use with caution as these drugs increase the bioavailability of lapatinib.
**Antacids, H2-antagonists, proton-pump inhibitors**: avoid if possible. Solubility of lapatinib is pH-dependent. Concomitant treatment with substances that increase gastric pH reduce lapatinib solubility and absorption.
**CYP3A4 and CYP2C8 substrates with narrow therapeutic windows** e.g. cisapride, pimozide, quinidine (all CYP3A4), repaglinide (CYP2C8): avoid concomitant treatment with lapatinib (causes increased exposure to these drugs).
**Pgp substrates with narrow therapeutic windows** e.g. digoxin: avoid concomitant treatment with lapatinib if possible. If concomitant treatment is essential, consider a reduction in the dose of the Pgp substrate.
**Grapefruit** and grapefruit juice should be avoided (increased exposure to lapatinib).

## Additional comments

This regimen is contraindicated if known or suspected dihydropyrimidine dehydrogenase (DPD) deficiency.

## References


- Summary of Product Characteristics Capecitabine Roche) accessed 10 Sept 2014 via www.medicines.org.uk
- Summary of Product Characteristics Lapatinib (GSK) accessed 10 Sept 2014 via www.medicines.org.uk
- NHS England Cancer Drug Fund List. Accessed 10 Sept 2014 via www.england.nhs.uk



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Date: 14 January 2015