**REGIMEN TITLE:** Lapatinib and capecitabine for breast cancer

**Funding arrangements to be set up and specified locally**

**Indication:**
Lapatinib in combination with Capecitabine is recommended as a treatment option for people with **advanced and/or metastatic Breast cancer** according LCNDG criteria:

- HER2 over-expressed (defined by IHC3+ or IHC2+ with gene amplification or gene amplification alone)
- Previous treatment with anthracycline and taxane and trastuzumab in the metastatic setting
- Left Ventricular Ejection Fraction within normal limits
- Patient able to tolerate and comply with oral dosage forms

**Regimen details:**
Lapatinib 1250mg po OD, continuously until disease progression.

Capecitabine 1000mg/m² po BD (morning and evening; equivalent to 2000 mg/m² total daily dose) for 14 days followed by a 7-day rest period.

**Administration:**
Lapatinib is available as a 250mg film coated tablet.
The daily dose of lapatinib should not be divided and should be taken either at least one hour before, or at least one hour after food. To minimise variability in the individual patient, administration of lapatinib should be standardised in relation to food intake, for example always to be taken one hour before a meal.

Capecitabine is available as 500mg and 150mg tablets, which are not scored or divisible. Tablets should be swallowed whole with water within 30 minutes after a meal. Tablets must NOT be crushed.
The manufacturer advises that patients unable to swallow the tablets may disperse each dose in warm water flavoured with a small amount of juice. However, there is no stability data to support this approach, therefore it remains the responsibility of the prescriber. Advise patient to stir with a spoon and drink immediately after disintegration. Appropriate measures for managing spillages and wastage need to be considered.

**Premedication:**
Not usually required.

**Frequency:**
Every 21 days, continued until disease progression or unacceptable toxicity.

**Anti-emetics:**
Low emetic potential
Specific individual drugs are stated in the Trust anti-emetic policy

**Supportive Care:**
Loperamide 4mg po stat then 2mg PRN for diarrhea (max. 16mg/day)
Anti-emetics (as per local policy) for nausea/vomiting
Topical emollients & Pyridoxine 50mg po TDS for Palmar Plantar Erythrodysesthesia
Mouthwashes (as per local policy) as required for stomatitis

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**Reason for Update:** Network Protocol Development

**Approved by Consultant:** Dr Anna Rigg

**Version:** 1

**Date:** 05-01-2011

**Supersedes:** All other versions

**Prepared by:** Jackie Chappell

**Checked by (Network Pharmacist):** J.Turner 26-01-2011
REGIMEN TITLE: Lapatinib and capecitabine for breast cancer
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Regular investigations:
- FBC Baseline & pre each cycle
- LFTs Baseline & pre each cycle
- U&Es Baseline & pre each cycle
- CrCl (Cockcroft & Gault) Baseline, then if clinically indicated
- MUGA/ECHO, LVEF Baseline & 3 monthly
- ECG Baseline and 3 monthly

Dose modifications:

**Haematological Toxicity**

<table>
<thead>
<tr>
<th>WBC &lt; 3.0 x 10^9/l</th>
<th>Delay for 1 week.</th>
</tr>
</thead>
<tbody>
<tr>
<td>or</td>
<td>Repeat FBC - If within normal parameters, resume</td>
</tr>
<tr>
<td>Neutrophils &lt; 1.5 x 10^9/l</td>
<td>treatment. Dose reduction should be considered if</td>
</tr>
<tr>
<td>or</td>
<td>myelosuppression results in delay of subsequent cycles</td>
</tr>
<tr>
<td>Platelets &lt;100 x 10^9/l</td>
<td></td>
</tr>
</tbody>
</table>

**Renal Impairment**

<table>
<thead>
<tr>
<th>Renal Impairment CrCl ml/min (Cockcroft &amp; Gault)</th>
<th>Lapatinib Dose</th>
<th>Capecitabine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>Give 100%</td>
<td>Give 100%</td>
</tr>
<tr>
<td>30 – 50</td>
<td>Give 100%</td>
<td>Give 75%</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>Caution</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

**Hepatic Impairment**

**Capecitabine:** In the absence of safety and efficacy data in patients with hepatic impairment, capecitabine use should be carefully monitored in patients with mild to moderate liver dysfunction. Administration of capecitabine should be interrupted if treatment-related elevations in bilirubin of >3.0 x ULN or treatment-related elevations in hepatic aminotransferases (ALT, AST) of >2.5 x ULN occur.

**Lapatinib:** should be discontinued if changes in liver function are severe and patients should not be retreated. Administration of lapatinib to patients with moderate to severe hepatic impairment should be undertaken with caution due to increased exposure to the medicinal product. Insufficient data are available in patients with hepatic impairment to provide a dose adjustment recommendation.

**Other non-haematological toxicities:**

**Capecitabine**

*Note that severe diarrhoea and/or severe mucositis early in the first treatment cycle can be the first presenting toxicity due to DPD enzyme deficiency, in which case potentially fatal neutropenia can quickly follow.*

Toxicity due to capecitabine administration may be managed symptomatically and/or modification of the dose (treatment interruption or dose reduction). Once the dose has been reduced, it should not be increased at a later...
REGIMEN TITLE: Lapatinib and capecitabine for breast cancer

Funding arrangements to be set up and specified locally.

Diarrhoea, abdo pain, N&V, Stomatitis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Appearance</th>
<th>Immediate action</th>
<th>Capecitabine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1st</td>
<td>Maintain dose</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>1st</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>2nd</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>75%</td>
</tr>
<tr>
<td>2</td>
<td>3rd</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>50%</td>
</tr>
<tr>
<td>2</td>
<td>4th</td>
<td>Discontinue treatment permanently</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1st</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>75%</td>
</tr>
<tr>
<td>3</td>
<td>2nd</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>50%</td>
</tr>
<tr>
<td>3</td>
<td>3rd</td>
<td>Discontinue treatment permanently</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1st</td>
<td>Discontinue or at consultant's discretion</td>
<td>50%</td>
</tr>
</tbody>
</table>

Palmar-Plantar Erythema

<table>
<thead>
<tr>
<th>Grade</th>
<th>Appearance</th>
<th>Immediate action</th>
<th>Capecitabine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1st</td>
<td>Maintain dose</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>1st</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>75%</td>
</tr>
<tr>
<td>2</td>
<td>2nd</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>50%</td>
</tr>
<tr>
<td>2</td>
<td>3rd</td>
<td>Discontinue treatment permanently</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1st</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>50%</td>
</tr>
<tr>
<td>3</td>
<td>2nd</td>
<td>Discontinue or at consultant's discretion</td>
<td>50%</td>
</tr>
</tbody>
</table>

Lapatinib

Non-haematological toxicities, other than cardiac/ lung events

<table>
<thead>
<tr>
<th>Grade</th>
<th>Appearance</th>
<th>Immediate action</th>
<th>Lapatinib Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1st</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>2nd</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>80% (1000mg od)</td>
</tr>
</tbody>
</table>

Cardiotoxicity:

Capecitabine: Coronary artery spasm is a recognised complication of capecitabine although the evidence base regarding aetiology, management & prognosis is not particularly strong. The incidence is estimated to be between 2% and 18%. Coronary artery spasm is usually reversible on discontinuing the treatment. Should a patient receiving capecitabine present with chest pains, stop the treatment. Standard investigation and treatment of angina may be required. If re-challenge is deemed necessary, this can be performed under close supervision, but should symptoms redevelop, capecitabine should be withdrawn permanently. Refer to Consultant to discuss.
Lapatinib: has been associated with reports of decreases in left ventricular ejection fraction (LVEF). Lapatinib has not been evaluated in patients with symptomatic cardiac failure. Caution should be taken if lapatinib is to be administered to patients with conditions that could impair left ventricular function (including co-administration with potentially cardiotoxic agents).

Lapatinib should be discontinued in patients with symptoms associated with decreased left ventricular ejection fraction (LVEF) that are National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade 3 or greater or if their LVEF drops below the institutions lower limit of normal. Lapatinib may be restarted at a reduced dose of 1000 mg/day when administered with capecitabine after a minimum of 2 weeks and if the LVEF recovers to normal and the patient is asymptomatic.

Prolongation of QT interval with lapatinib:
There has been no dedicated study to assess the potential for lapatinib to prolong the QT interval. A small, concentration dependent increase in QTc interval was observed in an uncontrolled, open-label dose-escalation study of lapatinib in advanced cancer patients, such that an effect on QT interval cannot be ruled out. Caution should be taken if lapatinib is administered to patients with conditions that could result in prolongation of QTc (including hypokalaemia, hypomagnesemia, congenital long QT syndrome, or co-administration of other medicines known to cause QT prolongation). Hypokalaemia or hypomagnesemia should be corrected prior to treatment. Electrocardiograms with QT measurement should be considered prior to administration of lapatinib and throughout treatment.

Interstitial lung disease/pneumonitis:
Lapatinib has been seen to cause interstitial lung disease/pneumonitis. Patients should be monitored for symptoms of pulmonary toxicity (dyspnoea, cough, fever) and treatment discontinued in patients who experience symptoms which are NCI CTCAE grade 3 or greater. Pulmonary toxicity may be severe and lead to respiratory failure. Fatal cases have been reported, causality of the deaths is uncertain.

Toxicities: Most commonly: diarrhoea, nausea, vomiting, dyspepsia, stomatitis, constipation, abdominal pain, anorexia, rash, hand-foot syndrome (palmar-plantar erythrodysesthesia), dry skin, pain in extremity and back, fatigue, mucosal inflammation, insomnia, headache, decreased left ventricular ejection fraction, interstitial lung disease/pneumonitis, hyperbilirubinaemia and hepatotoxicity


Capecitabine:
Warfarin/coumarin anticoagulants: Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking capecitabine concomitantly with coumarin-derived anticoagulants such as warfarin. Patients should be switched to low molecular weight heparin for the duration of therapy.
Phenytoin: Increased phenytoin plasma concentrations resulting in symptoms of phenytoin intoxication have been reported. Patients taking phenytoin concomitantly with capecitabine should have regular monitoring of phenytoin plasma concentrations.
Folinates: Folinic acid enhances the toxicity of capecitabine and reduces the maximum tolerated dose. It is possible that folic acid has the same effect. Avoid concomitant use.
Allopurinol: Allopurinol may reduce efficacy of capecitabine. Manufacturer advises avoid.
Lapatinib:
Lapatinib and capecitabine for breast cancer

Effects of other medicinal products on lapatinib

Lapatinib is predominantly metabolised by CYP3A

Co administration of lapatinib with strong inhibitors of CYP3A4 (e.g. ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, nefazodone) should be avoided. Co administration of lapatinib with moderate inhibitors of CYP3A4 should proceed with caution and clinical adverse reactions should be carefully monitored. Co administration of lapatinib with known inducers of CYP3A4 (e.g. rifampicin, rifabutin, carbamazepine, phenytoin or St John's Wort) should be avoided.

Lapatinib is a substrate for the transport proteins Pgp and BCRP. Inhibitors (ketoconazole, itraconazole, quinidine, verapamil, ciclosporin, erythromycin) and inducers (rifampicin, St John's Wort) of these proteins may alter the exposure and/or distribution of lapatinib

Concomitant treatment with substances that increase gastric pH should be avoided, as lapatinib solubility and absorption may decrease.

Effects of lapatinib on other medicinal products

Co administration of lapatinib with orally administered medicines with narrow therapeutic windows that are substrates of CYP3A4 (e.g. cisapride, pimozide and quinidine) should be avoided.

Co administration of lapatinib with medicines with narrow therapeutic windows that are substrates of CYP2C8 (e.g. repaglinide) should be avoided.

Co administration of lapatinib with orally administered digoxin resulted in an approximate 80% increase in the AUC of digoxin. Caution should be exercised when dosing lapatinib concurrently with medications with narrow therapeutic windows that are substrates of Pgp, and a reduction in the dose of the Pgp substrate should be considered.

Lapatinib inhibits the transport proteins BCRP and OATP1B1 in vitro. The clinical relevance of this effect has not been evaluated. It cannot be excluded that lapatinib will affect the pharmacokinetics of substrates of BCRP (e.g. topotecan) and OATP1B1 (e.g. rosuvastatin).

Interactions with food and drink

The bioavailability of lapatinib is increased up to about 4 times by food, depending on e.g. the fat content in the meal.

Grapefruit juice may inhibit CYP3A4 in the gut wall and increase the bioavailability of lapatinib and should therefore be avoided during treatment with lapatinib.

References:

SPC Xeloda and Tyverb accessed 16 October 2010 from www.medicines.org.uk
Micromedex review: Lapatinib
Geyer C. E. et al (2006); NEJM, 255(26):2733-2743