**Lapatinib and Capecitabine Therapy**

This protocol should be read in conjunction with NCCP protocol 00216 Capecitabine Monotherapy.

**INDICATIONS FOR USE:**

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Protocol Code</th>
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</thead>
<tbody>
<tr>
<td>Treatment of adult patients with breast cancer, whose tumours overexpress HER2 in combination with capecitabine for patients with advanced or metastatic disease with progression following prior therapy, which should have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting.</td>
<td>C50</td>
<td>00217a</td>
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</tbody>
</table>

**ELIGIBILITY:**

- Indications as above
- HER2 positive tumours as demonstrated by a validated test method
- ECOG status 0-2

**EXCLUSIONS:**

- Hypersensitivity to capecitabine, lapatinib or any of the excipients
- Known complete absence of dihydropyrimidine dehydrogenase (DPD) activity.
- Clinically significant cardiac disease
- History of severe and unexpected reactions to fluoropyrimidine therapy
- Pregnancy and lactation
- Severe leucopenia, neutropenia or thrombocytopenia
- Severe hepatic impairment
- Severe renal impairment (creatinine clearance below 30 ml/min [Cockcroft and Gault] at baseline)

**TESTS:**

**Baseline tests:** FBC, U&Es, LFTs, creatinine, cardiac function (ECG and ECHO or MUGA scan) if clinically indicated.

**Regular tests:** FBC, U&Es, LFTs, creatinine prior to each cycle. ECHO or MUGA repeated every 12 weeks unless there are signs of cardiac impairment where four to eight weeks may be more appropriate.
Weekly INR tests if patient is on warfarin until stable warfarin dose established, then INR prior to each cycle.

**Disease monitoring:**
Disease monitoring should be in line with the patient’s treatment plan and any other test/s as directed by the supervising Consultant.

**TREATMENT:**
*The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patient's individual clinical circumstances.*

Lapatinib is administered **once daily** continuously throughout the treatment cycle. Capecitabine is administered **daily in two doses** for two weeks (days 1-14) followed by a 7-day rest period on days 15-21. This 3-week period is considered a treatment cycle.

Treatment may be repeated every 21 days until disease progression or unacceptable toxicity develops.
DOSE MODIFICATIONS:

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-14</td>
<td>Capecitabine</td>
<td>1000mg/m² BD</td>
<td>PO with food or within 30 mins after food.</td>
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<tr>
<td></td>
<td>Lapatinib</td>
<td>1250mg daily</td>
<td>PO once daily at least 60mins before or after food</td>
</tr>
</tbody>
</table>

Lapatinib is available as 250mg tablets. Capecitabine is available in 150mg and 500mg tablets. The dose to be administered must take this into consideration. Detailed dose calculation tables for capecitabine are available in the Summary of Product Characteristics.

Missed doses of lapatinib should not be replaced; if a tablet is forgotten or vomited, normal dosing should be resumed at the next scheduled dose. Antacids, H₂ antagonists or proton pump inhibitors should not be taken within 2 hours of this medicine as they may interfere with its absorption.

- Any dose modification should be discussed with a Consultant.
- Dose modifications of lapatinib and capecitabine may occur independently.
- Refer to NCCP protocol 00216 for detailed information on dose modifications for toxicity due to capecitabine.
- Maximum treatment delay of 2 weeks is allowed for resolution of toxicity. If there is a delay of more than 2 weeks due to toxicity the involved drug should be discontinued permanently.
- At the beginning of a treatment cycle, if a treatment delay is indicated for either capecitabine or lapatinib then administration of all therapy should be delayed until the requirements for restarting all medicinal products are met.

Renal impairment:
No dose adjustment is necessary in patients with mild to moderate renal impairment. Caution is advised in patients with severe renal impairment as there is no experience of lapatinib in this population.

Hepatic Impairment:
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.

Table 1: Dose modification schedule for lapatinib based on adverse events

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Discontinue</th>
<th>Recommended dose modification</th>
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</thead>
<tbody>
<tr>
<td>Cardiac Toxicity</td>
<td></td>
<td>Discontinue lapatinib for a minimum of 2 weeks. It may be restarted at a reduced dose of 1000mg/day only if the LVEF recovers to normal and the patient is asymptomatic.</td>
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<tr>
<td>Symptoms associated with Grade ≥3 LVEF</td>
<td></td>
<td></td>
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<tr>
<td>Grade ≥3 pulmonary symptoms</td>
<td>Discontinue lapatinib</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td>Withhold treatment until diarrhoea resolves to grade 1 or less. Treatment may be re-initiated at a lower dose reduced from 1250mg/day to 1000mg/day</td>
</tr>
<tr>
<td>• Grade 1 or 2 with complicating features (moderate to severe abdominal cramping, nausea and vomiting ≥grade 2, decreased performance status, fever, sepsis, neutropenia, frank bleeding or dehydration)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Grade 3 (any)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td>Discontinue lapatinib</td>
</tr>
<tr>
<td>• Grade 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other toxicities ≥Grade 2</td>
<td></td>
<td>Consider discontinuation or interruption of dosing until toxicity improves to grade 1 or less. Treatment may be reinitiated at original dose of 1250mg/day.</td>
</tr>
<tr>
<td>First occurrence</td>
<td></td>
<td></td>
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<tr>
<td>Second occurrence</td>
<td></td>
<td>Treatment should be re-started at the lower dose of 1000mg/day when toxicity has resolved to grade 1 or less</td>
</tr>
</tbody>
</table>

SUPPORTIVE CARE:
EMETOGENIC POTENTIAL: Low. (Refer to local policy)

PREMEDICATIONS:
Not usually required.

TAKE HOME MEDICATIONS:
Medication may be required for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see local policy.

OTHER SUPPORTIVE CARE:
No specific recommendations.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions. The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Please refer to NCCP Protocol 00216 for information on adverse effects relating to capecitabine therapy.

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Cardiac toxicity**:
  - Lapatinib has been associated with reports of decreases in LVEF and QT prolongation. Evaluation of cardiac function, including LVEF determination, should be conducted for all patients prior to initiation of treatment with lapatinib and should continue to be evaluated during treatment to ensure that LVEF does not decline to an unacceptable level.
  - Caution should be taken if lapatinib is administered to patients with conditions that could result in prolongation of QTc.
  - Electrocardiograms with QT measurement should be considered prior to administration of lapatinib and throughout treatment.
- **Diarrhoea**: Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. Standard antidiarrhoeal treatments (e.g. loperamide) may be used.
- **Hepatotoxicity**: Hepatotoxicity has occurred with Tyverb use and may in rare cases be fatal. The hepatotoxicity may occur days to several months after initiation of treatment. At the initiation of treatment, patients should be advised of the potential for hepatotoxicity. Liver function (transaminases, bilirubin and alkaline phosphatase) should be monitored before the initiation of treatment and monthly thereafter, or as clinically indicated. Lapatinib dosing should be discontinued if changes in liver function are severe and patients should not be retreated.

DRUG INTERACTIONS:
Please refer to NCCP Protocol 00216 for information on drug reactions relating
to capecitabine therapy.

- Risk of drug interactions causing increased exposure to lapatinib with CYP3A4 inhibitors. Patients should also be counselled with regard to consumption of grapefruit and grapefruit juice.
- Risk of drug interactions causing decreased concentrations of lapatinib with CYP3A inducers.
- Co-administration of lapatinib with orally administered medicinal products with narrow therapeutic windows that are substrates of CYP3A4 and /or CYP2C8 should be avoided.
- Concomitant treatment with substances that increase gastric pH should be avoided, as lapatinib solubility and absorption may decrease.
- Current drug interaction databases should be consulted for more information.

**ATC CODE:**
Capecitabine - L01BC06
Lapatinib - L01XE07

**REIMBURSEMENT CATEGORY:**
Capecitabine and lapatinib are available for reimbursement under the High Tech Arrangements on the PCRS drug reimbursement schemes (October 2013).

**PRESCRIPTIVE AUTHORITY:**
The treatment plan must be initiated by a Consultant Medical Oncologist.

**REFERENCES:**
NCCP Protocol: Lapatinib and Capecitabine

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
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<tbody>
<tr>
<td>1</td>
<td>10/1/2015</td>
<td></td>
<td>Dr Maccon Keane</td>
</tr>
<tr>
<td>2</td>
<td>11/1/2017</td>
<td>Review Amended wording in exclusions with respect to DPD deficiency. Updated Adverse Reactions on hepatotoxicity</td>
<td>Dr Maccon Keane</td>
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</table>

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.