Lapatinib and Capecitabine Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
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.	C50	00217a	CDS

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 patients 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.

Day	Drug	Dose	Route	Cycle
1-14	Capecitabine	1000mg/m^2 Twice Daily[a, b, c]	PO with food or within 30 mins after food	Every 21 days
1-21 continuous	Lapatinib[d]	1250mg daily	PO once daily at least 60 mins before or after food	Continuous

[a] The dose to be administered should consider the available tablet strengths.
Reference to the NCCP DOSE BANDING TABLES for dosing of capecitabine - Available on the NCCP website.
Capecitabine tablets should be swallowed whole with plenty of water with food or within 30 minutes of eating. Tablets should not be crushed or cut.
[b] (Total daily dose = 2000mg/m^2)

[c] See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency.

[d] 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, H_2 antagonists or proton pump inhibitors should not be taken within 2 hours of this medicine as they may interfere with its absorption.

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 DPD deficiency
- Clinically significant cardiac disease
- History of severe and unexpected reactions to fluoropyrimidine therapy
- Pregnancy and lactation
- Severe hepatic or renal impairment
- Recent or concomitant treatment with brivudine

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profiles
- Cardiac function (ECG and ECHO or MUGA scan) if clinically indicated
- DPD testing prior to first treatment with capecitabine using phenotype and/or genotype testing unless patient has been previously tested
    - In patients with moderate or severe renal impairment, blood uracil levels used for dihydropyrimidine dehydrogenase (DPD) phenotyping should be interpreted with caution, as impaired kidney function can lead to increased uracil blood levels. Consequently, there is an increased risk for incorrect diagnosis of DPD deficiency, which may result in under dosing of 5-Fluorouracil or other fluoropyrimidines, leading to reduced treatment efficacy. Genotype testing for DPD deficiency should be considered for patients with renal impairment.

Regular tests:

- FBC, renal and liver profiles 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
- ECG if clinically indicated

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.

DOSE MODIFICATIONS:

- Consider a reduced starting dose in patients with identified partial DPD deficiency.
    - Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring.
- Any dose modification should be discussed with a Consultant.
- Dose modifications of lapatinib and capecitabine may occur independently.
- 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.

Haematological:

Table 1: Dose modification of capecitabine based on haematological toxicity

ANC (x 10^9/L)		Platelets(x 10^9/L)	1st Event Dose	2nd Event Dose	3rd Event Dose	4th Event Dose
≥ 1.5	and	≥ 75	100%	100%	100%	100%
1-1.49	or	50 – 74.9	Delay* then 100%	Delay* then 75%	Delay* then 50%	Discontinue
0.5-0.99	or	25- 49.9	Delay* then 75%	Delay* then 50%	Discontinue	Discontinue
< 0.5	or	< 25	Discontinue or delay* then 50%	Discontinue	Discontinue	Discontinue

*Delay until ANC ≥ 1.5x 10^9/L and platelets ≥ 75x10^9/L

Renal and Hepatic Impairment:

Table 2: Dose modification of lapatinib and capecitabine in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment
Lapatinib	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		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.
Capecitabine*	**CrCl (ml/min)**	**Dose**	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, regardless of the presence or absence of liver metastasis.
	≥30	100% dose	
	<30	Discontinue treatment	
*Reference Table 6 - for dose modification of capecitabine in treatment related hepatotoxicity			

Management of adverse events:

Table 3 shows the recommended dose modifications of capecitabine for those toxicities which are not individually specified:

Table 3: Capecitabine dose reduction schedule (three weekly cycle) based on toxicity

Toxicity grades*	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
• 1st appearance	Interrupt until resolved to grade 0-1	100%
• 2nd appearance		75%
• 3rd appearance		50%
• 4th appearance	Discontinue permanently	
Grade 3		
• 1st appearance	Interrupt until resolved to grade 0-1	75%
• 2nd appearance		50%
• 3rd appearance	Discontinue permanently	
Grade 4		
• 1st appearance	Discontinue permanently or If consultant deems it to be in patient's best interest to continue, interrupt until resolved to grade 0-1	50%
• 2nd appearance	Discontinue permanently	

*Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Table 4: Dose modification of capecitabine for diarrhoea

Grade*	Diarrhoea	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
0-1	Increase of 2 to 3 stools/day or nocturnal stools	Maintain dose level	Maintain dose level
2	Increase of 4 to 6 stools/day or nocturnal stools		
	• 1st appearance	Interrupt until resolved to grade 0-1	100%
	• 2nd appearance		75%
	• 3rd appearance		50%
	• 4th appearance	Discontinue permanently	
3	Increase of 7 to 9 stools/day or incontinence		
	• 1st appearance	Interrupt until resolved to grade 0-1	75%
	• 2nd appearance		50%
	• 3rd appearance	Discontinue permanently	
4	Increase of 10 or more stools/day or grossly bloody diarrhoea; may require parenteral support		
	• 1st appearance	Discontinue permanently or If consultant deems it to be in patient's best interest to continue, interrupt until resolved to grade 0-1	50%
	• 2nd appearance	Discontinue permanently	
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			

*Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Hand foot syndrome:

Table 5: Dose modification of capecitabine in hand foot syndrome

Toxicity Grade		Dose Modification
Grade 1	Skin changes (eg, numbness, dysesthesia, paresthesia, tingling, erythema) with discomfort not disrupting normal activities	100% Dose
Grade 2	Skin changes (eg, erythema, swelling) with pain affecting activities of daily living.	Withhold treatment until event resolves or decreases in intensity to grade 1.
Grade 3	Severe skin changes (eg, moist desquamation, ulceration, blistering) with pain, causing severe discomfort and inability to work or perform activities of daily living.	Withhold treatment until event resolves or decreases in intensity to grade 1. Subsequent doses of capecitabine should be decreased.

Treatment related hepatotoxicity

Table 6: Dose modification of capecitabine in treatment related hepatotoxicity

Bilirubin		ALT, AST	Dose Modification
> 3.0 x ULN	**or**	> 2.5 x ULN	Withhold treatment until bilirubin decreases to ≤ 3.0 x ULN or ALT, AST decrease to ≤ 2.5 x ULN

Table 7: Dose Modification of lapatinib for adverse events

Adverse reactions	Recommended dose modification
Cardiac Toxicity Symptoms associated with Grade ≥3 LVEF	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.
Grade ≥3 pulmonary symptoms	Discontinue apatinib
Diarrhoea • 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) • Grade 3 (any)	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.
Diarrhoea • Grade 4	Discontinue lapatinib
Other toxicities ≥Grade 2 First occurrence Second occurrence	Consider discontinuation or interruption of dosing until toxicity improves to grade 1 or less. Treatment may be reinitiated at original dose of 1250mg/day. Treatment should be re-started at the lower dose of 1000mg/day when toxicity has resolved to grade 1 or less.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Lapatinib: Minimal to Low **(Refer to local policy)**
Capecitabine: Minimal to Low **(Refer to local policy)**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

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.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Cardiac toxicity:**
  - Angina-like chest pain, tachycardia, arrhythmias, heart failure, myocardial infarction and cardiac arrest may occur with capecitabine especially in patients with a prior history of coronary artery disease.
  - 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.
- **Hepatoxicity:** Hepatotoxicity has occurred with lapatanib 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.
- **Dihydropyrimidine dehydrogenase (DPD) deficiency:** DPD is an enzyme encoded by the DPYD gene which is responsible for the breakdown of fluoropyrimidines. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidine-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity. Treatment with 5-Fluorouracil, capecitabine or tegafur-containing medicinal products is contraindicated in patients with known complete DPD deficiency. Consider a reduced starting dose in patients with identified partial DPD deficiency. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring. Therapeutic drug monitoring (TDM) of fluorouracil may improve clinical outcomes in patients receiving continuous 5-fluorouracil infusions.
- **Hand-foot syndrome (HFS)**: HFS, also known as palmar-plantar erythrodysaesthesia (PPE) is a common side effect associated with capecitabine (see Table 5 for dose modification of capecitabine for HFS).

DRUG INTERACTIONS:

- Capecitabine enhances the anticoagulant effect of warfarin. Patients taking coumarin derivative anticoagulants should be monitored regularly for alterations in their coagulation parameters and the anti-coagulant dose adjusted accordingly.
- Brivudine must not be administered concomitantly with capecitabine. Brivudine inhibits dihydropyrimidine dehydrogenase which can lead to increased fluoropyrimidine toxicity. Fatal cases have been reported following this drug interaction. There must be at least a 4-week waiting period between end of treatment with brivudine and start of capecitabine therapy.
- Patients taking phenytoin or fosphenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations.

- 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.

REFERENCES:

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Version	Date	Amendment	Approved By
1	10/01/2015		Prof Maccon Keane
2	11/01/2017	Review amended wording in exclusions with respect to DPD deficiency. Updated Adverse Reactions on hepatotoxicity	Prof Maccon Keane
3	16/01/2019	Updated to new NCCP regimen template. Inclusion of dose modification tables,adverse events and drug interactions for capecitabine	Prof Maccon Keane
4	11/03/2020	Standardisation of renal dose modifications for capecitabine	Prof Maccon Keane
5	21/08/2020	Updated exclusion criteria, baseline testing, dose modifications and adverse events with respect to DPD deficiency as per DHPC from HPRA June 2020	Prof Maccon Keane

		Updated Adverse events regarding palmar-plantar erythrodysaesthesia	
6	10/02/2021	Amended exclusions, regular tests, emetogenic potential and drug interactions.	Prof Maccon Keane
6a	03/11/2022	Standardised footnotes, amended anti-emetic guideline version number.	NCCP
6b	24/02/2025	Additional wording added to baseline testing section.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.