Capecitabine Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of patients with locally advanced or metastatic breast cancer	C50	00216a	N/A
Treatment of metastatic colorectal cancer	C18	00216b	N/A
Adjuvant treatment of patients following surgery of stage III colon cancer	C18	00216c	N/A
Adjuvant treatment of patients following surgery of stage II colon cancer[i]	C18	00216d	N/A
Adjuvant treatment of patients with metastatic colorectal cancer following complete resection[i]	C18	00216e	N/A
Adjuvant treatment of stage I to IIIB, triple negative breast cancer (TNBC) in patients with residual invasive disease after neoadjuvant chemotherapy treatment[i]	C50	00216f	N/A

*This is for post 2012 indications only

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.

Capecitabine is administered twice daily for two weeks (days 1-14) followed by a 7 day rest period on days 15-21. This 21 day (3-week) period is considered a treatment cycle.

Adjuvant treatment in patients with colon or triple negative breast cancer is recommended for a total of 6 months (8 cycles).

Treatment for metastatic disease is until disease progression or unacceptable toxicity develops.

Day	Drug	Dose	Route	Cycle
1-14	Capecitabine	1250mg/m^2 Twice Daily[a,b,c,d]	PO with food	Every 21 days

[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 .
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 = 2500mg/m^2)

[c] Starting dose of 1000 mg/m^2 twice daily may be considered for elderly patients, patients with a poor performance status or extensively pretreated patients.

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

ELIGIBILITY:

- Indications as above
- ECOG status 0-2

EXCLUSIONS:

- Hypersensitivity to capecitabine or any of the excipients
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency
- History of severe and unexpected reactions to fluoropyrimidine therapy
- Pregnancy and lactation
- 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 profile
- 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 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 profile 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.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- 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
- Toxicity due to capecitabine administration may be managed by symptomatic treatment 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 time
- For those toxicities considered by the treating physician to be unlikely to become serious or life-threatening, e.g. alopecia, altered taste, nail changes, treatment can be continued at the same dose without reduction or interruption

- Patients taking capecitabine should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs
- Doses of capecitabine omitted for toxicity are not replaced

Haematological:

- Initiation of treatment with capecitabine in patients with baseline neutrophil counts <1.5x10^9/L and/or thrombocyte counts of <100 x 10^9/L should be undertaken with caution.
- If unscheduled laboratory assessments during a treatment cycle show that the neutrophil count drops below 1x10^9/L or that the platelet count drops below 75x10^9/L, treatment with capecitabine should be interrupted.

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 capecitabine in renal and hepatic impairment

Renal Impairment		Hepatic Impairment*
CrCl (mL/min)	Dose	No dose adjustment is needed
51-80	No dose adjustment is needed	
30-50	75% of the original dose	
<30	Not recommended	
Haemodialysis	Not recommended	
*Reference Table 6 - for dose modification of capecitabine in treatment related hepatotoxicity		
Renal and hepatic dose modifications from Giraud et al 2023		

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	
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.

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.			

Hand foot syndrome:

Table 5: Dose modification of capecitabine in hand foot syndrome

Toxicity Grade		Dose Modification
Grade 1	Skin changes (e.g., numbness, dysesthesia, paresthesia, tingling, erythema) with discomfort not disrupting normal activities	100% Dose
Grade 2	Skin changes (e.g., 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 (e.g., 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

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL

- As outlined in NCCP Classification Document for Systemic Anti Cancer Therapy (SACT) Induced Nausea and Vomiting - available on the NCCP website

Capecitabine : Minimal to low (**Refer to local policy).**

For information:
Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - available on the NCCP website

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

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

REGIMEN SPECIFIC COMPLICATIONS:

- **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 5-Fluorouracil may improve clinical outcomes in patients receiving continuous 5-Fluorouracil infusions.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

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Version	Date	Amendment	Approved By
1	10/01/2015		Prof Maccon Keane
2	11/01/2017	Amended wording in exclusions with respect to DPD deficiency, Updated prescribing authority,	Prof Maccon Keane
3	19/12/2017	Applied new NCCP regimen template, clarified toxicity criteria for diarrhea and hand-foot syndrome	Prof Maccon Keane
4	08/01/2020	Reviewed. Update of drug interactions, exclusion criteria	Prof Maccon Keane
5	20/08/2020	Updated exclusion criteria, baseline testing, dose modifications and adverse events with respect to DPD deficiency as per DHPC from HPRA June 2020 Updated Adverse events regarding palmar-plantar erythrodysaesthesia	Prof Maccon Keane
6	24/08/2022	New indication added	Prof Maccon Keane
7	18/01/2023	Amended emetogenic potential	Prof Maccon Keane
8	27/01/2025	Reviewed. Updated baseline tests. Updated renal and hepatic dose modifications to align with Giraud et al 2023. Regimen updated in line with NCCP standardisation.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed indication for the use of capecitabine in Ireland. Patients should be informed of the unlicensed nature of this indication and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be aware of their responsibility in communicating any relevant information to the patient and also in ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.