Capecitabine and Oxaliplatin Therapy (XELOX)

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Adjuvant treatment of stage III (Dukes C) colon cancer after complete resection of the primary tumour	C18	00321a	Capecitabine N/A Oxaliplatin N/A
Treatment of advanced or metastatic colorectal cancer	C18	00321b	Capecitabine N/A Oxaliplatin N/A
Adjuvant stage II/III gastric adenocarcinoma post D2 gastrectomy	C18	00321c	Capecitabine N/A Oxaliplatin 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.

Oxaliplatin is administered on day 1 and capecitabine is taken 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: Treatment is recommended for 3 months (4 cycles) or 6 months (8 cycles) at the discretion of the prescribing consultant.

Treatment for metastatic disease is until disease progression or unacceptable toxicity develops.
Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Oxaliplatin[a]	130mg/m^2	IV infusion	500mL glucose 5% over 2 hours[b]	Every 21 days
1-14	Capecitabine	1000mg/m^2 Twice Daily [c, d, e]	PO with food	N/A	Every 21 days
[a] Oxaliplatin is incompatible with 0.9% NaCl. Do not piggyback or flush lines with 0.9% NaCl. For oxaliplatin doses ≤ 104mg use 250mL glucose 5%.					
[b] Increase infusion rate time to 4 – 6 hours in case of laryngopharyngeal dysaesthesia reaction.					
[c] The dose to be administered should consider the available tablet strengths. Please refer to the NCCP DOSE BANDING TABLES Available on the NCCP website for 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. [d] (total daily dose = 2000mg/m^2)					
[e] See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency					

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ELIGIBILITY:

- Indications as above
- ECOG status 0-1

CAUTION:

Use with caution in patients with clinically significant cardiovascular disease

EXCLUSIONS:

- Hypersensitivity to capecitabine, oxaliplatin or any of the excipients
- Known complete dihydropyrimdine dehydrogenase (DPD) deficiency
- Pregnancy and lactation
- Severe leucopenia, neutropenia or thrombocytopenia
- Severe hepatic impairment
- Peripheral neuropathy with functional impairment prior to first cycle

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- INR tests if patient is on warfarin (as 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 profile prior to each cycle
- INR tests if patient is on warfarin (as 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:

- Any dose modification should be discussed with a Consultant.
- Consider a reduced starting dose of capecitabine 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.
- Dose reductions to manage chemotherapy-induced adverse reactions for oxaliplatin and capecitabine and are outlined in Tables 1-8 below

Haematological:

Patients with baseline neutrophil counts< $1.5x10^9$/L and/or platelet counts of<100 x 10^9/L should not be treated with capecitabine.

Table 1: Dose reduction levels for oxaliplatin and capecitabine for non-neurologic toxicity

Drug	Dose	Dose -1	Dose-2	Dose-3
Oxaliplatin	130 mg/m^2	100 mg/m^2	85 mg/m^2	Discontinue
Capecitabine	1000mg/m^2 BD	750 mg/m^2 BD	500 mg/m^2 BD	Discontinue

Table 2: Dose Modifications for Haematological Toxicity

Prior to a Cycles (DAY 1)	TOXICITY		Dose Level for Subsequent Cycles	
	Grade	**ANC (x 10^9/L)**	**Oxaliplatin**	**Capecitabine**
• If ANC< 1.2 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 2 times • ANC ≥ 1.2 within 2 weeks, proceed with treatment at the dose level noted across from the lowest ANC result of the delayed week(s). • If ANC remains < 1.2 after 2 weeks discontinue treatment	1	≥ 1.2	Maintain dose level	Maintain dose level
	2	1-1.19	Maintain dose level	Maintain dose level
	3	0.5-0.99	↓ 1 dose level	↓ 1 dose level
	4	<0.5	↓ 2 dose levels	↓ 2 dose levels
	Grade	**Platelets (x10^9/L)**	**Oxaliplatin**	**Capecitabine**
• If platelets < 75 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 2 weeks • Platelets ≥ 75 within 2weeks, proceed with treatment at the dose level noted across from the lowest platelets result of the delayed week(s). • If platelets remains <75 after 2 weeks discontinue treatment	1	≥ 75	Maintain dose level	Maintain dose level
	2	50-74.9	Maintain dose level	Maintain dose level
	3	10-49.9	↓ 1 dose level	↓ 1 dose level
	4	<10	↓ 2 dose levels	↓ 2 dose levels

Renal and Hepatic Impairment:

Table 3: Dose modification of capecitabine and oxalipatin in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment
	CrCl (mL/min)	Dose	
Capecitabine*	51-80	No dose adjustment is needed	No dose adjustment is needed.
	30-50	75% of original dose	
	<30	Not recommended	
	Haemodialysis	Not recommended	
Oxaliplatin	≥30	No dose adjustment is needed.	No dose adjustment is needed
	<30	Consider 50% of the original dose	
	Haemodialysis	Consider 50% of the original dose, Haemodialysis within 90 minutes after administration	
*Reference Table 5 for dose modification of capecitabine in treatment related hepatotoxicity			

Management of adverse events:

Non-Haematological and Non-neurological Toxicities:

If Grade 2, 3 or 4 toxicities occur, daily administration of capecitabine should be immediately interrupted until these symptoms resolve or decrease in intensity to grade 1.

Table 4: Dose Modifications for Non-Haematologic, Non-Neurologic Toxicity

Prior to a Cycle (Day 1)			Dose Level for Subsequent Cycles	
Diarrhoea	**Grade ****		**Oxaliplatin**	**Capecitabine**
• If diarrhoea grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks maximum 2 times. • If diarrhoea < Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the Highest grade experienced. • If diarrhoea remains Grade 2 after 2 weeks, discontinue treatment.	1	Increase of < 4 stools/day over baseline	Maintain dose level	Maintain dose level
	2	Increase of 4 to 6 stools/day over baseline	Maintain dose level	Maintain dose level
	3	Increase of ≥7 stools/day	Maintain dose level	↓ 1 dose level
	4	[a]Increase of 10 or more stools/day or grossly bloody diarrhoea; may require parenteral support. Urgent intervention indicated	↓ 1 dose level	↓ 2 dose levels*
Stomatitis	**Grade ****		**Oxaliplatin**	**Capecitabine**
• If stomatitis ≥ Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times. • If stomatitis < Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the highest Grade experienced. • If stomatitis remains ≥Grade 2 after 2 weeks, discontinue treatment.	**1**	Asymptomatic or mild symptoms; intervention not indicated	Maintain dose level	Maintain dose level
	2	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Maintain dose level	Maintain dose level
	3	Severe pain; interfering with oral intake	Maintain dose level	↓ 1 dose level
	4	[a]As above but mucosal necrosis and/or requires	↓ 1 dose level	↓ 2 dose levels*

		enteral support, dehydration. Urgent intervention indicated		
Palmar-Plantar Erythrodysaesthesia (Hand-Foot Syndrome)	**Grade ****		**Oxaliplatin**	**Capecitabine**
• If hand-foot skin reaction ≥ Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times. • If hand-foot skin reaction is < Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the highest Grade experienced • If hand-foot skin reaction remains ≥ Grade 2 after 2 weeks, discontinue treatment.	**1**	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Maintain dose level	Maintain dose level
	2	Skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Maintain dose level	Maintain dose level
	3	Severe skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting self care ADL	Maintain dose level	↓ 1 dose level
***If treatment with capecitabine is discontinued, then oxaliplatin is also discontinued.** **AE Grading CTCAEv5.0				

Treatment related hepatotoxicity

Table 5: Dose modification of capecitabine in treatment related hepatotoxicity

Bilirubin		ALT, AST	Dose Modification
> 3 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 6: Dose modification of oxaliplatin due to oxaliplatin induced peripheral neuropathy

Toxicity Grade	Dose Modification of oxaliplatin
Grade 1	100%
Grade 2 paraesthesia persisting until next cycle	Reduce dose to 100mg/m^2
Grade 3 paraesthesia > 7 days but resolved before next cycle	Reduce dose to 100mg/m^2
Grade 3 paraesthesia persisting until next cycle	Discontinue oxaliplatin
Grade 4 of any duration	Discontinue oxaliplatin

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

Oxaliplatin - Moderate **(Refer to local policy).**
Capecitabine - Low-Minimal (**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 unless patient has had a previous hypersensitivity.

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

- **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.

DRUG INTERACTIONS:

- Consult current drug interaction databases and relevant SmPC for details.

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Version	Date	Amendment	Approved By
1	03/06/2016		Prof Maccon Keane
2	30/05/2018	Applied new NCCP regimen template, Amended wording in exclusions with respect to DPD deficiency, updated dosing in renal impairment and clarified toxicity criteria for diarrhoea, stomatitis and hand-foot syndrome	Prof Maccon Keane
3	07/09/2018	Added in the new indication 'Adjuvant Stage II/III gastric adenocarcinoma post D2 gastrectomy'	Prof Maccon Keane
4	12/02/2020	Updated treatment table for oxaliplatin administration Updated recommended dose modifications for oxaliplatin in renal impairment	Prof Maccon Keane
5	11/03/2020	Updated recommended dose modifications for capecitabine in renal impairment	Prof Maccon Keane
6	24/08/2020	Reviewed. 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

7	23/09/2022	Amended adjuvant treatment duration	Prof Maccon Keane
8	16/10/2024	Reviewed. Addtion of table 6 - Dose Modification of oxaliplatin due to oxaliplatin induced peripheral neuropathy. Update to footnotes in treatment table. Updated eligibility section. Updated exclusions section. Updated renal and hepatic dose modifications table to align with Giraud et al 2023. Updated regimen in line with NCCP standardisation.	Prof Maccon Keane
8a	12/05/2025	Additional wording added to baseline testing section.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.