Capecitabine and Oxaliplatin Therapy (XELOX)

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Adjuvant treatment of stage III (Dukes C) colon cancer after complete resection of the primary tumour	C18	00321a	Capecitabine CDS Oxaliplatin Hospital
Treatment of advanced or metastatic colorectal cancer	C18	00321b	Capecitabine CDS Oxaliplatin Hospital
Adjuvant Stage II/III gastric adenocarcinoma post D2 gastrectomy	C18	00321c	Capecitabine CDS Oxaliplatin Hospital

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 a total of 6 months (8 cycles).

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

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Oxaliplatin[a]	130mg/m^2	IV infusion	500ml glucose 5% over 2hrs[b]	Every 21 days
1-14	Capecitabine[c,d]	1000mg/m^2 Twice Daily[e]	PO with food	N/A	Every 21 days
[a]Oxaliplatin is incompatible 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 Here for capecitabine. Tablets should be swallowed whole with plenty of water within 30 minutes of eating. Tablets should not be crushed or cut.					
[d]See dose modifications section for patients with identified partial DPD deficiency					
[e]total daily dose = 2000mg/m^2					

ELIGIBILITY:

- Indications as above
- ECOG status 0-1
- Expected survival > 3 months

CAUTION:

Use with caution in patients with clinically significant cardiovascular disease

EXCLUSIONS:

- Hypersensitivity to capecitabine, oxaliplatin or any of the excipients
- Known complete DPD deficiency
- Pregnancy and lactation
- Severe leucopenia, neutropenia or thrombocytopenia
- Severe hepatic impairment
- Severe renal impairment (creatinine clearance below 30ml/min [Cockcroft and Gault] at baseline
- 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

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:

- 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.
- 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:

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 in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment
	CrCl (ml/min)	Dose	
Capecitabine*	≥30	100% 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	Discontinue treatment	
Oxaliplatin	>30	Treat at normal dose and monitor renal function	Little information available. Probably no dose reduction necessary. Clinical decision.
	<30	Contraindicated	
*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 enteral support, dehydration. Urgent intervention indicated	↓ 1 dose level	↓ 2 dose levels*

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				

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

OXALIPLATIN

Neurologic Toxicity

Table 6: Dose reduction levels for oxaliplatin for Neurologic Toxicity

Drug	Dose	Dose -1	Dose-2	Dose-3
Oxaliplatin	130 mg/m^2	100 mg/m^2	65 mg/m^2	Discontinue

If patient has both neurologic and non-neurologic toxicity, the final dose of oxaliplatin is the LOWER of the dose adjustments (i.e. if haematologic toxicity mandates dose –2 reduction (85 mg/m^2) and neurologic toxicity mandates dose –2N reduction (65 mg/m^2), then 65 mg/m^2 is given

Table 7: Dose Modifications for Neurologic Toxicity

Toxicity Grade	Duration of Toxicity		Persistent (present at start of next cycle)
	1-7 days	> 7 days	
1	Maintain dose level	Maintain dose level	Maintain dose level
2	Maintain dose level	Maintain dose level	↓ 1 neurotoxicity dose level
3	↓ 1 neurotoxicity dose level	↓ 1 neurotoxicity dose level	Discontinue therapy
4	Discontinue therapy	Discontinue therapy	Discontinue therapy
Laryngo-pharyngeal dysaesthesia	Increase infusion time from 2 to 6 hrs	N/A	N/A

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Oxaliplatin - Moderate
Capecitabine - Low-Minimal (**Refer to local policy).**

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 / REGIMEN SPECIFIC COMPLICATIONS

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

- **Diarrhoea and dehydration:** This may be dose limiting. Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated.
- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Cardiotoxicity:** 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.
- **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**), also known as palmar-plantar erythrodysaesthesia (PPE), is a common side effect associated with capecitabine (see Table 4 for dose modification of capecitabine for HFS).
- **Laryngopharyngeal dysaesthesia:** An acute syndrome of laryngopharyngeal dysaesthesia occurs in 1% - 2% of patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm. Symptoms are often precipitated by exposure to cold. Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome.
- **Extravasation:** Oxaliplatin causes irritation if extravasated (Refer to local policy**).**
- **Venous occlusive disease:** A rare but serious complications that has been reported in patients (0.02%) receiving oxaliplatin in combination with fluorouracil. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Patients should be instructed to report any jaundice, ascites or hematemesis immediately.

- **Haemolytic Ureamic Syndrome (HUS):** Oxaliplatin therapy should be interrupted if HUS is suspected: hematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135 micromol/L. If HUS is confirmed, oxaliplatin should be permanently discontinued.

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.
- Sorivudine inhibits dihydropyrimidine dehydrogenase thus increasing its toxicity. Therefore, capecitabine must not be administered concomitantly with sorivudine or its chemically related analogues.
- Patients taking phenytoin or fosphenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Capecitabine - L01BC06
Oxaliplatin - L01XA03

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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

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.