Modified FOLFOX-6 Therapy-14 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Indicator
Adjuvant treatment of stage II or III colon cancer after complete resection of primary tumour	C18	00209a	
Metastatic colorectal carcinoma	C18	00209b	

If a reimbursement indicator (e.g. ODMS, CDS[i]) is not defined, the drug and its detailed indication have not gone through the formal reimbursement process as legislated for in the Health (Pricing and Supply of Medical Goods) Act 2013.

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.

Adjuvant treatment is administered every 14 days for 12 cycles or until disease progression or unacceptable toxicity develops. For patients with low risk disease (T1-3,N1) adjuvant treatment may be administered every 14 days for 6 cycles (1).

For metastatic colon carcinoma treatment is administered continuously or until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Oxaliplatin	85mg/m^2	IV infusion	250-500ml glucose 5% over 2hrs	Every 14 days
2	1	Folinic Acid (Calcium leucovorin)	400mg/m^2	IV infusion	250ml glucose 5% over 2hrs	Every 14 days
Flush line with glucose 5% before administering 5-FU						
3	1	Fluorouracil (5-FU)	400mg/m^2	IV BOLUS		Every 14 days
4	1	Fluorouracil	2400mg/m^2	Continuous IV infusion	Over 46h in glucose 5% or 0.9% NaCl.	Every 14 days
Oxaliplatin is incompatible with 0.9% NaCl. For oxaliplatin doses ≤ 104mg use 250ml glucose 5%. Oxaliplatin administration must always precede the administration of 5-FU. Oxaliplatin may be given at the same time as Folinic Acid *(Calcium Leucovorin)* using a Y connector.						
Folinic Acid *(Calcium Leucovorin)* must be administered prior to fluorouracil. It enhances the effects of fluorouracil by increasing fluorouracil binding to the target enzyme thymidylate synthetase. Acute neurotoxicity is common with oxaliplatin and can be precipitated on exposure to the cold therefore in this regimen patients should NOT suck on ice chips during the bolus injection of fluorouracil.						

ELIGIBILTY:

- Indications as above
- ECOG 0-2
- Adequate haematological, renal and liver status

CAUTION:

Use with caution in patients with

- Previous pelvic radiotherapy
- Recent MI
- Uncontrolled angina, hypertension, cardiac arrhythmias, CHF
- In patients with baseline greater than 3 loose bowel movements (BM) per day (in patients without colostomy or ileostomy)
- Symptomatic peripheral neuropathy

EXCLUSIONS:

- Hypersensitivity to oxaliplatin or any of the excipients
- Severe renal impairment (creatinine clearance < 30ml/min)
- Breast feeding
- 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:

- Blood, liver and renal profile
- ECG (if patient has compromised cardiac function)

Regular tests:

- Blood, liver and renal profile prior to each cycle
- Evaluate for peripheral neuropathy every 2 cycles

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
- The following dose reductions should be used when calculating FOLFOX dose reductions for patients with toxicities**.**

Table 1: Dose Reduction Levels for All Toxicity

	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2	Discontinue
Folinic Acid *(Calcium Leucovorin)*	400 mg/m^2	400 mg/m^2	400 mg/m^2	Discontinue
Fluorouracil bolus	400 mg/m^2	320 mg/m^2	260 mg/m^2	Discontinue
Fluorouracil infusion	2400 mg/m^2	1900 mg/m^2	1500 mg/m^2	Discontinue

Note: Folinic acid is delayed or omitted if bolus fluorouracil is delayed or omitted

Haematological:

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**	**Fluorouracil**
• If ANC< 1.5 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 4 weeks • ANC ≥ 1.5 within 4 weeks, proceed with treatment at the dose level noted across from the lowest ANC result of the delayed week(s). • If ANC remains <1.5 after 4 weeks discontinue treatment	1	≥ 1.5	Maintain dose level	Maintain dose level
	2	1.0-1.49	Maintain dose level	Maintain dose level
	3	0.5-0.99	↓ 1 dose level	Maintain dose level
	4	<0.5	↓ 1 dose level	Omit bolus and ↓1 infusion dose level
	Grade	**Platelets (x10^9/L)**	**Oxaliplatin**	**Fluorouracil**
• If platelets < 75 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 4 weeks • Platelets ≥ 75 within 4 weeks, proceed with treatment at the dose level noted across from the lowest platelets result of the delayed week(s). • If platelets remains <75 after 4 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	Maintain dose level
	4	<10	↓ 2 dose levels	Maintain dose level

Renal and Hepatic Impairment:

Table 3. Recommended dose modification for 5-FU in patients with renal or hepatic impairment

Drug	Renal impairment		Hepatic impairment			
Oxaliplatin	**CrCl(ml/min)**	**Dose**	Little information available. Probably no dose reduction necessary Clinical decision			
	>20	Treat at normal dose and monitor renal function				
	<20	Dose reduce				
5-FU	Consider dose reduction in severe renal impairment only		**Bilirubin (micromol/L)**		**AST**	**Dose**
			<85		<180	100%
			>85	or	>180	Cl
			Clinical decision. Moderate hepatic impairment; reduce initial dose by 1/3. Severe hepatic impairment, reduceinitial dose by 1/2. Increase dose if no toxicity			

Management of adverse events:

Table 4: Dose modification schedule based on adverse events

Adverse reactions	Discontinue	Recommended dose modification
*Peripheral neuropathy Grade 2 present at start of cycle Grade 3 • First occurrence • 2nd occurrence • Persistent Grade 4	 ↓ 1 dose level ↓1 dose level Discontinue oxaliplatin Discontinue oxaliplatin	Reduce oxaliplatin by 1 dose level
Laryngo-pharyngeal dysaethesia		Increase infusion time from 2 to 6 hrs
Stomatitis		Delay treatment until stomatitis reaches level of grade 1 or less
Grade 4 Diarrhoea		In adjuvant treatment reduce oxaliplatin dose to 75mg/m^2 and in metastatic treatment reduce oxaliplatin dose to 65mg/m^2 in addition to any 5FU dose reductions required.
Unexplained respiratory symptoms e.g. Non-productive cough, dyspnoea, crackles or radiological pulmonary infiltrates	Discontinue oxaliplatin until interstitial disease or pulmonary fibrosis excluded.	

*Neuropathy may be partially or wholly reversible after discontinuation of therapy; patients with good recovery from Grade 3 (not Grade 4) neuropathy may be considered for re- challenge with oxaliplatin, with starting dose one level below that which they were receiving when neuropathy developed.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate (**Refer to local policy).**

PREMEDICATIONS: Not usually required unless the patient has had a previous hypersensitivity.

OTHER SUPPORTIVE CARE:
Anti-diarrhoeal treatment **(Refer to 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.

- **Platinum Hypersensitivity**: Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. In case of anaphylactic manifestations the infusion should be interrupted immediately and an appropriate symptomatic treatment started. Re-administration of oxaliplatin to such patients is contraindicated.
- **Laryngopharyngeal dysesthesia:** An acute syndrome of pharyngolaryngeal dysesthesia 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.
- **Gastrointestinal toxicity:** Patients treated with fluorouracil should be closely monitored for diarrhea and managed appropriately.
- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
- **Myocardial ischaemia and angina:** Cardiotoxicity is a serious complication during treatment with fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with fluorouracil, should be carefully monitored during therapy.
- **Dihydropyrimidine dehydrogenase (DPD) deficiency:** Rare, life-threatening toxicities such as stomatitis, mucositis, neutropenia, neurotoxicity and diarrhoea have been reported following administration of fluoropyrimidines (e.g. fluorouracil and capecitabine). Severe unexplained toxicities require investigation prior to continuing with treatment.
- **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.
- **Palmar Plantar Erythrodysesthesia (PPE):** This has been reported as an unusual complication of high dose bolus or protracted continuous therapy with fluorouracil.

DRUG INTERACTIONS:

- Marked elevations of prothrombin time and INR have been reported in patients stabilized on warfarin therapy following initiation of fluorouracil regimes.
- Concurrent administration of fluorouracil and phenytoin may result in increased serum levels of phenytoin

- Caution should be taken when using fluorouracil in conjunction with medications which may affect dihydroprimidine dehydrogenase activity
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Oxaliplatin	-	L01XA03
5-Fluorouracil	-	L01BC02
Folinic acid	-	V03AF03

REFERENCES:

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2. André T, Boni C et al. Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer. N Engl J Med 2004;350:2343-2351
3. Tournigand C, André T et al. FOLFIRI followed by FOLFOX6 or the reverse Sequence in Advanced Colorectal Cancer : A Randomized GERCOR Study. J Clin Oncol 2004; Vol 22 No.2: 229-237
4. Eloxatin ®Summary of Product Characteristics Accessed 20 /9/2013 Available at: http://www.imb.ie/images/uploaded/swedocuments/LicenseSPC_PA0540-148-001_04092012155136.pdf
5. Fluorouracil 50mg/ml infusion for injection. Accessed May 2017 Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1390-015-001_26042017095409.pdf

Version	Date	Amendment	Approved By
1	10/1/2015		Prof Maccon Keane
2	24/2/2015	Infusor table update	Prof Maccon Keane
3	01/03/2017	Reviewed	Prof Maccon Keane
4	27/09/2017	Updated with new NCCP regimen template and updated dosing for adjuvant treatment and haematological toxicity	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes

Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/