FOLFOX-6 Modified Therapy-14 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Adjuvant treatment of stage II or III colon cancer after complete resection of primary tumour.	C18	00209a	Hospital
Metastatic colorectal carcinoma	C18	00209b	Hospital
Advanced or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction.	C15 C16	00209c	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.

Colon Carcinoma:

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.

Gastric/oesophageal carcinoma: Treatment is administered continuously or until disease progression or unacceptable toxicity develops (maximum of 12 cycles).

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	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
3	1	Fluorouracil	400mg/m^2	IV BOLUS		Every 14 days
4	1	*Fluorouracil	2400mg/m^2	Continuous IV infusion	Over 46h in 0.9% NaCl.	Every 14 days
Oxaliplatin is incompatible with 0.9% NaCl. Do not piggyback or flush lines with normal saline For oxaliplatin doses ≤ 104mg use 250ml glucose 5%. Increase infusion rate time to 4 – 6 hours in case of laryngopharyngeal dysaesthesia reaction 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.						
*See dose modifications section for patients with identified partial DPD deficiency						

ELIGIBILITY:

- 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
- Known complete DPD deficiency

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)
- DPD testing prior to first treatment with 5-Fluorouracil using phenotype and/or genotype testing unless patient has been previously tested

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:

- **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.
- 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 modifications 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			
	≥30	Treat at normal dose and monitor renal function				
	<30	Contraindicated				
5-Fluorouracil	Consider dose reduction in severe renal impairment only		**Bilirubin (micromol/L)**		**AST**	**Dose**
			<85		<180	100%
			>85	or	>180	Contraindicated
			Clinical decision. Moderate hepatic impairment; reduce initial dose by 1/3. Severe hepatic impairment, reduce initial 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 dysaesthesia		Increase infusion time from 2 to 6 hrs
Stomatitis		Delay treatment until stomatitis reaches level of grade 1 or less
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.

Management of adverse events:

Table 5: Dose modification of Modified FOLFOX-6 for diarrhoea

Prior to a Cycles (DAY 1)	TOXICITY		Dose Level for Subsequent Cycles	
	Grade	Diarrhoea	Oxaliplatin	Fluorouracil
• If diarrhoea greater than or equal to Grade 2 on Day 1 of cycle, hold treatment. Perform weekly checks, maximum 4 times. • If diarrhoea is less than Grade 2 within 4 weeks, proceed with treatment at the dose level noted across from the highest Grade experienced. • If diarrhoea remains greater than or equal to Grade 2 after 4 weeks, discontinue treatment.	1	Increase of 2-3 stools/day, or mild increase in loose watery colostomy output	Maintain dose level	Maintain dose level
	2	Increase of 4-6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Maintain dose level	Maintain dose level
	3	Increase of 7-9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	Maintain dose level	↓ 1 dose level of IV push and infusional fluorouracil
	4	Increase of 10 or more stools/day or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	↓ 1 dose level	↓ 1 dose level of IV push and infusional fluorouracil

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Oxaliplatin: Moderate (**Refer to local policy).**
Fluorouracil: Low (**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.

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.

Oxaliplatin

- **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 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.

5-Fluorouracil

- **Gastrointestinal toxicity:** Patients treated with fluorouracil should be closely monitored for diarrhea and managed appropriately.
- **Hand-foot syndrome (HFS),** also known as palmar-plantar erythrodysaesthesia (PPE) has been reported as an unusual complication of high dose bolus or protracted continuous therapy for 5-fluorouracil.
- **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:** 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:

- 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
- Fluorouracil is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5-FU-metabolising enzyme dihydropyrimidine dehydrogenase (DPD).
- Caution should be taken when using fluorouracil in conjunction with medications which may affect dihydropyrimidine dehydrogenase activity.
- Current drug interaction databases should be consulted for more information.

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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
5	31/08/2018	Updated with new indication and standardisation of treatment table.	Prof Maccon Keane

6	2/03/2019	Updated management of diarrhoea	Prof Maccon Keane
7	12/02/2020	Standardisation of treatment table. Update exclusions, drug interactions and emetogenic potential	Prof Maccon Keane
8	26/02/2020	Standardisation of treatment table.	Prof Maccon Keane
9	20/08/2020	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

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