FOLFOX-4 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	00210a	Hospital
Metastatic colorectal carcinoma	C18	00210b	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.

Adjuvant treatment is administered every 14 days for 12 cycles or until disease progression or unacceptable toxicity develops.

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

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Oxaliplatin [a]	85mg/m^2	IV infusion	500mL glucose 5% over 2 hours	Every 14 days
2	1	Folinic Acid [b] (Calcium leucovorin)	200mg/m^2	IV infusion	250mL glucose 5% over 2 hours	Every 14 days
3	1 and 2	5-Fluorouracil	400mg/m^2	IV BOLUS		Every 14 days
4	1 and 2	5-Fluorouracil[c]	600mg/m^2	Continuous IV infusion	Over 22 hours in 0.9% NaCl	Every 14 days

[a] 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-Fluorouracil.
Oxaliplatin may be given at the same time as Folinic Acid *(Calcium Leucovorin)* using a Y connector.

[b] Folinic Acid *(Calcium Leucovorin)* must be administered prior to 5-Fluorouracil. It enhances the effects of 5-Fluorouracil by increasing 5-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 5-Fluorouracil.

[c] See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (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, congestive heart failure (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, 5-Fluorouracil, folinic acid 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 dihydropyrimidine dehydrogenase (DPD) deficiency

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, 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
    - 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, 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:

- 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)*	200 mg/m^2	200 mg/m^2	200 mg/m^2	Discontinue
5-Fluorouracil bolus	400 mg/m^2	320 mg/m^2	260 mg/m^2	Discontinue
5-Fluorouracil infusion	600 mg/m^2	500 mg/m^2	400 mg/m^2	Discontinue

Note: Folinic acid is delayed or omitted if bolus 5-Fluorouracil is delayed or omitted

Haematological:

Table 2. Dose Modifications for Haematological Toxicity

Prior to a Cycle (DAY 1)	TOXICITY		Dose Level for Subsequent Cycles	
	Grade	**ANC (x10^9/L)**	**Oxaliplatin**	**5-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**	**5-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 remain <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: Dose modification in 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	Recommended dose modification
*Peripheral neuropathy Grade 2 present at start of cycle Grade 3 • First occurrence • 2nd occurrence • Persistent Grade 4	 Reduce oxaliplatin by 1 dose level ↓ 1 dose level ↓ 1 dose level Discontinue oxaliplatin Discontinue oxaliplatin
Laryngopharyngeal dysaesthesia	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 5-Fluorouracil 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:

Oxaliplatin: Moderate **(Refer to local policy).**
5-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.

- **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 laryngopharyngeal 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 5-Fluorouracil should be closely monitored for diarrhoea 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 5-Fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with 5-Fluorouracil, should be carefully monitored during therapy.
- **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.
- **Extravasation:** Oxaliplatin causes irritation if extravasated **(Refer to local policy).**
- **Venous occlusive disease:** A rare but serious complication that has been reported in patients (0.02%) receiving oxaliplatin in combination with 5-Fluorouracil. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Patients should be instructed to report any jaundice, ascites or haematemesis 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.
- **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.

DRUG INTERACTIONS:

- Marked elevations of prothrombin time and INR have been reported in patients stabilized on warfarin therapy following initiation of 5-Fluorouracil regimens.
- Concurrent administration of 5-Fluorouracil and phenytoin may result in increased serum levels of phenytoin.
- 5-Fluorouracil is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5-Fluorouracil-metabolising enzyme DPD.
- Caution should be taken when using 5-Fluorouracil in conjunction with medications which may affect DPD activity.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	10/01/2015		Prof Maccon Keane
2	24/02/2015	Infusor table update	Prof Maccon Keane
3	01/03/2017	Reviewed.	Prof Maccon Keane
4	4/10/2017	Updated with new NCCP regimen template and updated dosing in haematological toxicity	Prof Maccon Keane
5	09/10/2019	Reviewed. Standardisation of treatment table. Updated exclusions, dose modifications, drug interactions, emetogenic potential.	Prof Maccon Keane
6	09/01/2020	Updated recommended dose modifications for oxaliplatin in renal impairment. updated infusion fluids for Folinic Acid (Calcium leucovorin) Updated exclusion criteria for DPD.	Prof Maccon Keane
7	26/02/2020	Standardisation of treatment table	Prof Maccon Keane
8	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
9	18/11/2021	Reviewed. Updated Exclusions.	Prof Maccon Keane
9a	21/11/2023	Formatting changes and grammatical corrections.	NCCP
9b	24/02/2025	Updated baseline tests with additional wording.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie