FLOX Therapy

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	00486a	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.

- Folinic acid is administered weekly for 6 consecutive weeks (on days 1, 8, 15, 22, 29, and 36 of the treatment cycle), followed by a 2-week rest period.
- 5-Fluorouracil is administered as an intravenous bolus 1 hour after the folinic acid infusion has begun, and is administered weekly for 6 weeks (on days 1, 8, 15, 22, 29, and 36 of the treatment cycle), followed by a 2-week rest period.
- Oxaliplatin is administered as a 2-hour infusion before folinic acid and 5-fluorouracil on days 1, 15, and 29 of the treatment cycle.
- Treatment is administered for three 8-week cycles of therapy for a total treatment duration of 24 weeks (6 months) unless disease progression or unacceptable toxicity develops.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1, 15 and 29	Oxaliplatin	85mg/m^2	IV infusion	500ml Glucose 5% over 2 hours	Every 8 weeks for 3 cycles
2	1, 8, 15, 22, 29, 36	Folinic acid (Calcium leucovorin)	500mg/m^2	IV infusion	250mls Glucose 5% Over 2 hours	Every 8 weeks for 3 cycles
3	1, 8, 15, 22, 29, 36	*5-Fluorouracil	500mg/m^2	IV bolus to be given 1 hr after start of the folinic acid infusion		Every 8 weeks for 3 cycles
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. The 5-Fluorouracil bolus can then be administered immediately on completion of the folinic acid infusion.						
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

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:

- 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

Regular tests:

- FBC, liver and renal profile prior to each treatment
- 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.

Haematological:

Table 1: Dose modifications for haematological toxicity

ANC (x10^9/L)		Platelets (x10^9/L)	Dose
<1	and/or	<100*	Delay treatment until recovery
<0.5	and/or	<50	Delay treatment until recovery and consider reducing oxaliplatin and fluorouracil by 25% for subsequent cycles
Febrile Neutropenia			

*Given the slower accumulation of thrombocytopenia with oxaliplatin, the treating clinician may decide to proceed with treatment when platelets are 75 to 100 x 10^9/L

Renal and Hepatic Impairment:

Table 2: Dose modifications in renal and hepatic impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal impairment</th><th colspan="4">Hepatic impairment</th></tr>
<tr><td rowspan="3">Oxaliplatin</td><td>CrCl (ml/min)</td><td>Dose</td><td colspan="4" rowspan="2">Little information available.
Probably no dose reduction necessary
Clinical decision</td></tr>
<tr><td>>30</td><td>Treat at normal dose and monitor renal function</td></tr>
<tr><td><30</td><td>Contraindicated</td><td colspan="4">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.</td></tr>
<tr><td rowspan="3">5-Fluorouracil</td><td colspan="2" rowspan="3">Consider dose reduction in severe renal impairment only</td><td>Bilirubin (micromol/L)</td><td></td><td>AST</td><td>Dose</td></tr>
<tr><td><85</td><td></td><td><180</td><td>100%</td></tr>
<tr><td>>85</td><td>or</td><td>>180</td><td>Contraindicated</td></tr>
</table>

Management of adverse events:

Table 3: Dose Modifications for Adverse Events

Adverse reactions	Recommended dose modification
*Peripheral neuropathy Grade 2 present at start of cycle	Reduce oxaliplatin by 25% if persistent, consider omitting oxaliplatin
Grade 3 or Grade 4	Discontinue oxaliplatin
Laryngo-pharyngeal dysaesthesia	Increase infusion time from 2 to 6 hrs
Mucositis and Stomatitis or Diarrhoea Grade 2 • 1st occurrence • 2nd occurrence • 3rd occurrence • 4th occurrence	Delay treatment until toxicity has resolved to grade 1 or less and reduce dose for subsequent cycles as follows • No dose reduction • Reduce oxaliplatin and 5-fluorouracil by 25% • Reduce oxaliplatin and 5-fluorouracil by 50% • Withhold chemotherapy
Grade 3 or 4 • 1st occurrence • 2nd occurrence	Delay treatment until toxicity has resolved to grade 1 or less and reduce dose for subsequent cycles as follows • Reduce oxaliplatin and 5-fluorouracil by 50% • Withhold chemotherapy
Hand foot syndrome Grade 2 • 1st occurrence • 2nd occurrence • 3rd occurrence • 4th occurrence	Delay treatment until toxicity has resolved to grade 1 or less and reduce dose for subsequent cycles as follows • No dose reduction • Reduce 5-fluorouracil by 25% • Reduce 5-fluorouracil by 50% • Omit 5-fluorouracil
Grade 3 or 4 • 1st occurrence • 2nd occurrence	Delay treatment until toxicity has resolved to grade 1 or less and reduce dose for subsequent cycles as follows • Reduce 5-fluorouracil by 50% • Omit 5-fluorouracil

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

PREMEDICATIONS: Not usually required unless 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

- **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.
- **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.
- **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

Flourouracil:

- **Gastrointestinal toxicity:** Patients treated with fluorouracil should be closely monitored for diarrhea and managed appropriately.
- **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.
- **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 (see table 3 for dose modifications).

DRUG INTERACTIONS:

- Marked elevations of prothrombin time and INR have been reported in patients stabilized on warfarin therapy following initiation of fluorouracil regimens.
- 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.

ATC CODE:

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

REFERENCES:

1. Kuebler JP, Wie and HS et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol. 2007 Jun 1;25(16):2198-204.
1. Krens S D, Lassche,Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Onco/2019;20:e201-08.
2. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V2 2019 Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp%20antiemetic%20classification%20document%20v1%202018.pdf
3. HPRA Direct Healthcare Professional Communication. 5-Fluorouracil (i.v.), capecitabine and tegafur containing products: Pre-treatment testing to identify DPD-deficient patients at increased risk of severe toxicity. Accessed Aug 2020 Available at: https://www.hpra.ie/docs/default-source/default-document-library/important-safety-information-from-marketing-authorisation-holders-of-products-containing-5-fluorouracil-(i-v-)-capecitabine-and-tegafur-as-approved-by-the-hpra.pdf?sfvrsn=0
4. Oxaliplatin (Eloxatin ®) Summary of Product Characteristics. Accessed May 2020 Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0540-148-001_23042019151332.pdf
5. Fluorouracil 50mg/ml infusion for injection. Accessed May 2020 . Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1390-015-001_26042017095409.pdf

Version	Date	Amendment	Approved By
1			Prof Maccon Keane
2	01/05/19	Updated treatment table for folinic acid	Prof Maccon Keane
3	09/10/2019	Updated tests, exclusions, drug interactions.	Prof Maccon Keane
4	07/01/2020	Standardisation of treatment table. Updated exclusion criteria. Updated recommended dose modifications for oxaliplatin in renal impairment.	Prof Maccon Keane
5	26/02/2020	Standardisation of treatment table.	Prof Maccon Keane
6	27/05/2020	Regimen reviewed.	Prof Maccon Keane
7	2/9/2020	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. Treatment table updated regarding 5-Fluorouracil bolus administration.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.