FLOX Therapy

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>*Reimbursement Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant treatment of stage II or III colon cancer after complete resection of primary tumour</td>
<td>C18</td>
<td>00486a</td>
<td>Hospital</td>
</tr>
</tbody>
</table>

*If the reimbursement status is not defined, the indication has yet to be assessed through the formal HSE reimbursement process.

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 patient's 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 is 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.

<table>
<thead>
<tr>
<th>Admin. Order</th>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1, 15 and 29</td>
<td>Oxaliplatin</td>
<td>85mg/m²</td>
<td>IV infusion</td>
<td>500ml Glucose 5% over 2 hours</td>
<td>Every 8 weeks for 3 cycles</td>
</tr>
<tr>
<td>2</td>
<td>1, 8, 15, 22, 29, 36</td>
<td>Folinic acid (Calcium leucovorin)</td>
<td>500mg/m²</td>
<td>IV infusion</td>
<td>Over 2 hours</td>
<td>Every 8 weeks for 3 cycles</td>
</tr>
<tr>
<td>3</td>
<td>1, 8, 15, 22, 29, 36</td>
<td>5-Fluorouracil</td>
<td>500mg/m²</td>
<td>IV bolus to be given 1 hr after start of the folinic acid infusion</td>
<td>Every 8 weeks for 3 cycles</td>
<td></td>
</tr>
</tbody>
</table>

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

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

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:
- Any dose modification should be discussed with a Consultant.

Haematological:
Table 1: Dose modifications for haematological toxicity

<table>
<thead>
<tr>
<th>ANC (x10^9/L)</th>
<th>Platelets (x10^9/L)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 and/or &lt;100*</td>
<td>Delay treatment until recovery</td>
<td></td>
</tr>
<tr>
<td>&lt;0.5 and/or &lt;50</td>
<td>Delay treatment until recovery and consider reducing oxaliplatin and fluorouracil by 25% for subsequent cycles</td>
<td></td>
</tr>
</tbody>
</table>

*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>
<thead>
<tr>
<th>Drug</th>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin</td>
<td>CrCl(ml/min)</td>
<td>Dose</td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
<td>Treat at normal dose and monitor renal function</td>
</tr>
<tr>
<td></td>
<td>&lt;20</td>
<td>Dose reduce</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-Fluorouracil</td>
<td>Consider dose reduction in severe renal impairment only</td>
<td>&gt;85 or &gt;180</td>
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</tbody>
</table>
Management of adverse events:
Table 3: Dose Modifications for Adverse Events

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Recommended dose modification</th>
</tr>
</thead>
</table>
| *Peripheral neuropathy  
Grade 2 present at start of cycle  
Grade 3 or Grade 4 | Reduce oxaliplatin by 25% if persistent, consider omitting oxaliplatin  
Discontinue oxaliplatin |
| Laryngopharyngeal dysaesthesia | Increase infusion time from 2 to 6 hrs |
| Mucositis and Stomatitis or Diarrhoea  
Grade 2  
- 1st occurrence  
- 2nd occurrence  
- 3rd occurrence  
- 4th occurrence  
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  
No dose reduction  
Reduce oxaliplatin and 5-fluorouracil by 25%  
Reduce oxaliplatin and 5-fluorouracil by 50%  
Withhold chemotherapy  
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  
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  
No dose reduction  
Reduce 5-fluorouracil by 25%  
Reduce 5-fluorouracil by 50%  
Omit 5-fluorouracil  
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
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.

- 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.
- **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.
- **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 Uremic 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 regimens.
- 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:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>ATC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin</td>
<td>L01XA03</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>L01BC02</td>
</tr>
<tr>
<td>Folinic acid</td>
<td>V03AF03</td>
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</table>

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician. and is subject to HSE’s terms of use available at [http://www.hse.ie/eng/Disclaimer](http://www.hse.ie/eng/Disclaimer). This information is valid only on the day of printing, for any updates please check [www.hse.ie/NCCPchemoregimens](http://www.hse.ie/NCCPchemoregimens).
REFERENCES:


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<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>Prof Maccon Keane</td>
</tr>
</tbody>
</table>

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

1 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/