FLOT Therapy-14 day

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>*Reimbursement Indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of locally advanced (≥T2) and/or nodal positive (N+) resectable gastric adenocarcinoma</td>
<td>C16</td>
<td>00344a</td>
<td></td>
</tr>
<tr>
<td>Treatment of locally advanced (≥T2) and/or nodal positive (N+) resectable adenocarcinoma of the oesophagogastric junction</td>
<td>C16</td>
<td>00344b</td>
<td></td>
</tr>
</tbody>
</table>

If a reimbursement indicator (e.g. ODMS, CDS) 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 patient's individual clinical circumstances.

DOCEtaxel, oxaliplatin, folinic Acid and 5-fluorouracil are administered on Day 1 of a 14 day cycle.
Four neoadjuvant cycles are administered prior to surgery over 8 weeks and four adjuvant cycles are administered post-surgery over 8 weeks.
Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

<table>
<thead>
<tr>
<th>Order of Admin</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</td>
<td>DOCEtaxel</td>
<td>50mg/m²</td>
<td>IV infusion</td>
<td>≥250ml 0.9% sodium chloride or 5% glucose over 60min</td>
<td>Every 14 days</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>bOxaliplatin</td>
<td>85mg/m²</td>
<td>IV infusion</td>
<td>250-500ml glucose 5% over 2hrs²</td>
<td>Every 14 days</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Folinic Acid (Calcium leucovorin)</td>
<td>200mg/m²</td>
<td>IV infusion</td>
<td>250ml glucose 5% over 2hrs</td>
<td>Every 14 days</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>Fluorouracil</td>
<td>2600mg/m²</td>
<td>Continuous IV infusion</td>
<td>Over 24h in 0.9% NaCl or glucose 5%</td>
<td>Every 14 days</td>
</tr>
</tbody>
</table>

Secondary prophylaxis with G-CSF is recommended for patients who experience febrile neutropenia or treatment interruptions because of neutropenia or leucopenia.

³75-185mg dose use 250ml infusion bag. For doses > 185mg use 500ml infusion bag
Use non-PVC equipment

¹Oxaliplatin 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.
³Increase infusion rate time for oxaliplatin to 4–6 hours in case of laryngopharyngeal dysaesthesia reaction.

ELIGIBILITY:

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

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EXCLUSIONS:

- Hypersensitivity to DOCEtaxel, oxaliplatin, 5-FU or any of the excipients
- Severe hepatic impairment

USE with CAUTION:

- Peripheral neuropathy ≥ Grade 2

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- Blood, renal and liver profile

Regular tests:

- Blood, renal and liver profile prior to each cycle.
- Evaluate for peripheral neuropathy every 2 cycles or as clinically indicated

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>
<thead>
<tr>
<th>ANC (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>WBC (x 10^9/L)</th>
<th>Dose of DOCEtaxel and Oxaliplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 and</td>
<td>≥ 100</td>
<td>≥ 3</td>
<td>100% Dose</td>
</tr>
</tbody>
</table>

Thrombocytopenia with bleeding

Dose reduce to 75%

Febrile neutropenia:

- First occurrence
- Second occurrence (despite use of G-CSF)
- Further occurrences

Consider the use of G-CSF

Dose reduce to 75%

Dose reduce to 50%

G-CSF secondary prophylaxis recommended for patients who experience febrile neutropenia or treatment interruptions because of neutropenia or leucopenia
Renal and Hepatic Impairment:

### Table 2: Dose modification in renal and hepatic impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal impairment</th>
<th>Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOCEtaxel</td>
<td>No dose reduction necessary</td>
<td>See Table 3 below</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Moderate renal impairment 100% Monitor renal function. Dose adjust according to toxicity</td>
<td>Little information available. Probably no dose reduction necessary. Clinical decision.</td>
</tr>
<tr>
<td></td>
<td>Cr Cl&lt;20ml/min Dose reduce — Clinical decision</td>
<td></td>
</tr>
<tr>
<td>5-FU</td>
<td>Consider dose reduction in severe renal impairment only</td>
<td>Clinical decision. Moderate hepatic impairment; reduce initial dose by 1/3. Severe hepatic impairment, reduce initial dose by 1/2.</td>
</tr>
</tbody>
</table>

### Table 3: Dose modification of DOCEtaxel in hepatic impairment

<table>
<thead>
<tr>
<th>Alkaline Phosphatase</th>
<th>AST and/or ALT</th>
<th>Serum Bilirubin</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 2.5 ULN and &gt; 1.5 ULN</td>
<td>&lt;= ULN</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>&gt; 6 ULN and/or &gt; 3.5 ULN (AST and ALT)</td>
<td>&gt; ULN</td>
<td>Stop treatment unless strictly indicated and should be discussed with a Consultant.</td>
<td></td>
</tr>
</tbody>
</table>

### Non-haematological toxicity:

### Table 4: Dose modification schedule based on adverse events

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade &gt;2 Non-haematological toxicity</td>
<td>Decrease dose of all drugs to 75%</td>
</tr>
<tr>
<td>First occurrence</td>
<td>Decrease dose of all drugs to 50%</td>
</tr>
<tr>
<td>Second occurrence</td>
<td></td>
</tr>
</tbody>
</table>

### Oxaliplatin induced neuropathy:

### Table 5: Dose modification of oxaliplatin due to oxaliplatin induced neuropathy

<table>
<thead>
<tr>
<th><em>Peripheral neuropathy</em></th>
<th>*</th>
<th>Reduce oxaliplatin to 65mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2 present at start of cycle</td>
<td></td>
<td>Reduce oxaliplatin to 65mg/m²</td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td>Reduce oxaliplatin to 50mg/m²</td>
</tr>
<tr>
<td>• First occurrence</td>
<td></td>
<td>Discontinue oxaliplatin</td>
</tr>
<tr>
<td>• 2nd occurrence</td>
<td></td>
<td>Discontinue oxaliplatin</td>
</tr>
<tr>
<td>• Persistent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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.*
NCCP Chemotherapy Regimen

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate (Refer to local policy).

PREMEDICATIONS:

- Dexamethasone 8 mg PO twice daily for 3 days, starting one day prior to each DOCEtaxel administration unless contraindicated. Patient must receive minimum of 3 doses pre-treatment.
- Consideration may be given, at the discretion of the prescribing consultant, to the use of a single dose of dexamethasone 20mg IV immediately before chemotherapy where patients have missed taking the oral premedication dexamethasone as recommended by the manufacturer (4,5).

OTHER SUPPORTIVE CARE:
Medication may be required for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see 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: Most frequent adverse reaction. Fever or other evidence of infection must be assessed promptly and treated appropriately. Frequent blood count monitoring should be conducted in all patients treated with DOCEtaxel. DOCEtaxel should be administered when the neutrophil count is > 1.5x10^9 cells/L.
- Extravasation: DOCEtaxel causes pain and tissue necrosis if extravasated. Oxaliplatin causes irritation if extravasated. (Refer to local extravasation guidelines).

DOCEtaxel

- Neutropenic Enterocolitis: A number of cases of neutropenic enterocolitis have been reported in patients treated with DOCEtaxel in France (6). This is a known and rare side effect of DOCEtaxel which may affect up to one in 1,000 people)
- Hypersensitivity Reactions: Patients should be observed closely for hypersensitivity reactions especially during the first and second infusions of DOCEtaxel. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of DOCEtaxel, thus facilities for the treatment of hypotension and bronchospasm should be available. However, severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of DOCEtaxel and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with DOCEtaxel.
- Fluid Retention: Dexamethasone premedication must be given to reduce the incidence and severity of fluid retention with DOCEtaxel. It can also reduce the severity of the hypersensitivity reaction.

5-Fluorouracil

- Gastrointestinal toxicity: Patients treated with fluorouracil should be closely monitored for diarrhoea and managed appropriately.
- Dihydropyrimidine dehydrogenase (DPD) deficiency: Rare, life-threatening toxicities such as stomatitis, mucositis, neutopenia, 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.

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

<table>
<thead>
<tr>
<th>NCCP Regimen: FLOT Therapy-14 day</th>
<th>Published: 08/09/2017</th>
<th>Version number: 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour Group: Gastrointestinal</td>
<td>ISMO Contributor: Prof Maccon Keane</td>
<td></td>
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<tr>
<td>NCCP Regimen Code: 00344</td>
<td>Page 4 of 6</td>
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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.

**DRUG INTERACTIONS:**
- Risk of drug interactions causing increased concentrations of DOCEtaxel with CYP3A inhibitors and decreased concentrations of DOCEtaxel with CYP3A inducers.
- 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.
- Current drug interaction databases should be consulted for more information.

**ATC CODE:**
- DOCEtaxel L01CD02
- S-FU L01BC02
- Folinic acid V03AF03
- Oxaliplatin L01XA03

**REFERENCES:**
1. Perioperative chemotherapy with DOCEtaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capcitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): A multicenter, randomized phase 3 trial. 2017 ASCO Annual Meeting Abstract 4004 J Clin Oncol 35, 2017 (suppl; abstr 4004)

Version | Date       | Amendment                                                                 | Approved By            
--------|------------|---------------------------------------------------------------------------|------------------------
1        | 18/08/2017 |                                                                        | Prof Maccon Keane      
2        | 04/10/2017 | Amended dose modifications for haematological toxicity                    | Prof Maccon Keane      

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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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/