DOCEtaxel / Cyclophosphamide (TC) Therapy-21 day

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 patients with high risk node-positive or node-negative early operable breast cancer.</td>
<td>C50</td>
<td>00250a</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.

DOCEtaxel and cyclophosphamide are administered once every 21 days for 4-6 cycles.
If radiation therapy is required, it is given following completion of chemotherapy.

Admin Order | Day | Drug      | Dose   | Route   | Diluent & Rate
-------------|-----|-----------|--------|---------|----------------|
1            | 1   | DOCEtaxel | 75mg/m²| IV infusion | ²250ml 0.9% sodium chloride over 60min |
2            | 1   | Cyclophosphamide | 600mg/m² | IV Bolus | ²250ml 0.9% sodium chloride infusion over 30 min |

Primary prophylaxis with G-CSF should be considered to reduce the risk of neutropenic complications (See Adverse Effects/Regimen Specific Complications)

²75-185mg dose use 250mL infusion bag. For doses> 185mg use 500mL infusion bag
Use non-PVC equipment.

²Cyclophosphamide may also be administered as an IV bolus over 5-10 mins. Order of administration may be reversed.

ELIGIBILITY:
- Indications as above.
- ECOG status 0-1.
- Adequate haematological parameters (ANC > 1.5 x 10⁹/L, platelets > 90 x 10⁹/L).
- Adequate renal and hepatic function.
- Life expectancy > 3 months.

EXCLUSIONS:
- Hypersensitivity to DOCEtaxel, cyclophosphamide or to any of the excipients
- Severe liver impairment.
- Pregnancy or lactation.
- Grade ≥2 peripheral neuropathy.
PRESCRIPTIVE AUTHORITY:
The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:
Baseline tests:
FBC, Renal and Liver profile

Regular tests:
FBC, Renal and Liver profile* as clinically indicated
*See Adverse Effects/Regimen specific complications for guidelines regarding hepatic dysfunction

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 modification 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>≥ 1.5</td>
<td>and</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>1 – 1.49</td>
<td>or</td>
<td>70 to 90</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>or</td>
<td>&lt; 70</td>
</tr>
</tbody>
</table>

Delay until ANC > 1.5 and platelets > 90 then give 75% of previous cycle doses.

Febrile Neutropenia:
Table 2: Dose modification for febrile neutropenia

<table>
<thead>
<tr>
<th>Event</th>
<th>Dose reduction option</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st episode</td>
<td>75% of previous cycle dose if day 1 ANC ≥ 1.5 and platelets ≥ 100</td>
</tr>
<tr>
<td>2nd episode</td>
<td>50% of original cycle dose if day 1 ANC ≥ 1.5 and platelets ≥ 100</td>
</tr>
<tr>
<td>3rd episode</td>
<td>Discontinue protocol.</td>
</tr>
</tbody>
</table>

Note: Post one episode of ANC 1-1.49 x 10^9/L or first episode of febrile neutropenia another consideration is the addition of G-CSF as secondary prophylaxis.
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Renal and Hepatic Impairment:

Table 3: 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>Alkaline Phosphatase and AST and/or ALT</td>
</tr>
<tr>
<td></td>
<td>&gt;2.5 ULN and &gt;1.5 ULN</td>
<td>Serum bilirubin</td>
</tr>
<tr>
<td></td>
<td>&gt; 6 ULN and &gt;3.5 ULN (AST and ALT)</td>
<td>Dose of DOCEtaxel</td>
</tr>
<tr>
<td></td>
<td>&gt; ULN</td>
<td>Stop treatment unless strictly indicated and should be discussed with a consultant</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>CrCl (mL/min)</td>
<td>Dose</td>
</tr>
<tr>
<td>&gt;20</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>10-20</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>50%</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 of DOCEtaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 skin reaction</td>
<td>Decrease dose to 60mg/m²</td>
</tr>
<tr>
<td>Grade &gt;2 peripheral neuropathy</td>
<td>If the patient continues to experience these reactions at 60 mg/m², the treatment should be discontinued</td>
</tr>
<tr>
<td>Grade 3 or 4 stomatitis</td>
<td></td>
</tr>
</tbody>
</table>

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 (3,4).

OTHER SUPPORTIVE CARE:

- Patients should have an increased fluid intake of 2-3 litres on day 1 to prevent haemorrhagic cystitis associated with cyclophosphamide.

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 > 1.5x10⁹ cells/L.
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- **Neutropenic Enterocolitis**: A number of cases of neutropenic enterocolitis have been reported in patients treated with DOCEtaxel in France (5). 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. If hypersensitivity reactions occur, minor symptoms such as flushing or localized cutaneous reactions do not require interruption of therapy. 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.

- **Extravasation**: DOCEtaxel causes pain and tissue necrosis if extravasated. (Refer to local extravasation guidelines).

- **Hepatic Dysfunction**: DOCEtaxel undergoes hepatic metabolism. Hepatic dysfunction (particularly elevated AST) may lead to increased toxicity and usually requires a dose reduction.

- **SIADH**: (syndrome of inappropriate secretion of antidiuretic hormone): may occur in patients receiving cyclophosphamide, resulting in hyponatremia, dizziness, confusion or agitation, unusual tiredness or weakness. This syndrome is more common with doses >50 mg/kg and may be aggravated by administration of large volumes of fluids to prevent hemorrhagic cystitis. The condition is self-limiting although diuretic therapy may be helpful in the situation when the patient has stopped urinating (especially if this occurs during the first 24 hours of cyclophosphamide therapy). Susceptible patients should be monitored for cardiac decompensation.

**DRUG INTERACTIONS:**
- Risk of drug interactions causing increased concentrations of DOCEtaxel with CYP3A inhibitors. These drugs also decrease the conversion of cyclophosphamide to both its active and inactive metabolites. Patients should also be counselled with regard to consumption of grapefruit juice.
- Risk of drug interactions causing decreased concentrations of DOCEtaxel with CYP3A inducers. These drugs also increase the conversion of cyclophosphamide to both its active and inactive metabolites.
- Cyclophosphamide inhibits cholinesterase metabolism of suxamethonium which may prolong its neuromuscular blocking effect.
- Current drug interaction databases should be consulted for more information.

**ATC CODE:**

- DOCEtaxel L01CD02
- Cyclophosphamide L01AA01

**REFERENCES:**


<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29/04/2015</td>
<td></td>
<td>Dr Maccon Keane</td>
</tr>
<tr>
<td>2</td>
<td>30/05/2015</td>
<td>Modification of premedication regimen</td>
<td>Dr Maccon Keane</td>
</tr>
<tr>
<td>3</td>
<td>28/06/2017</td>
<td>Updated with new NCCP template, clarified title and dosing in renal and hepatic impairment and admin order Clarified use of G-CSF and updated re neutropenic enterocolitis</td>
<td>Prof Maccon Keane</td>
</tr>
<tr>
<td>4</td>
<td>16/01/2019</td>
<td>Updated dose modification of docetaxel in hepatic impairment table Standardised administration of docetaxel and cyclophosphamide</td>
<td>Prof Maccon Keane</td>
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Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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/