DOCEtaxel /Cyclophosphamide (TC) Therapy-21 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement status
Adjuvant treatment of patients with high risk node-positive or node-negative early operable breast cancer.	C50	00250a	Hospital

**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 patients individual clinical circumstances.

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

Admin Order	Day	Drug	Dose	Route	Diluent & Rate
1	1	DOCEtaxel	75mg/m^2	IV infusion	[a]250ml 0.9% NaCl over 60min
2	1	Cyclophosphamide	600mg/ m^2	IV infusion[b]	[b]250ml 0.9% NaCl over 30 min
Primary prophylaxis with G-CSF should be considered to reduce the risk of neutropenic complications (See Adverse Effects/Regimen Specific Complications)					
[a]75-185mg dose use 250mL infusion bag. For doses> 185mg use 500mL infusion bag **Use non-PVC equipment.**					
[b] Cyclophosphamide may also be administered as an IV bolus over 5-10mins . Order of administration may be reversed					

ELIGIBILTY:

- Indications as above.
- ECOG status 0-1.
- Adequate haematological parameters (ANC > 1.5 x 10^9/L, platelets > 90 x 10^9/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

ANC (x10^9/L)		Platelets (x10^9/L)	Dose
≥ 1.5	and	> 90	100%
1 – 1.49	or	70 to 90	75%
< 1	or	< 70	Delay until ANC > 1.5 and platelets > 90 then give 75% of previous cycle doses.

Febrile Neutropenia:

Table 2: Dose modification for febrile neutropenia

Event	Dose reduction option
1st episode	75% of previous cycle dose if day 1 ANC ≥ 1.5 and platelets ≥ 100
2nd episode	50% of original cycle dose if day 1 ANC ≥1.5 and platelets ≥ 100
3rd episode	Discontinue protocol.

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.

Renal and Hepatic Impairment:

Table 3: Dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment					
DOCEtaxel	No dose reduction necessary		**Alkaline Phosphatase**		**AST and/or ALT**		**Serum bilirubin**	**Dose of DOCEtaxel**
			>2.5 ULN	and	≥1.5 ULN			75mg/m^2
			> 6 ULN	And /or	> 3.5 ULN (AST and ALT)	And	> ULN	Stop treatment unless strictly indicated and should be discussed with a consultant
Cyclophosphamide	**CrCl (mL/min)**	**Dose**	Severe impairment: Clinical Decision					
	>20	100%						
	10-20	75%						
	<10	50%						

Non-Haematological Toxicity:

Table 4: Dose modification schedule based on adverse events

Adverse reactions	Recommended dose modification of DOCEtaxel
Grade 3 skin reaction	Decrease dose to 60mg/m^2 If the patient continues to experience these reactions at 60 mg/m^2, the treatment should be discontinued
Grade >2 peripheral neuropathy	
Grade 3 or 4 stomatitis	

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 >

1.5x10^{9}cells/L.

- **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:

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2. Jones S et al. DOCEtaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735. J Clin Oncol 2009;27(8):1177-83.
3. Chouhan et al. Single premedication dose of dexamethasone 20mg IV before DOCEtaxel administration. J Oncol Pharm Practice 2010;17(3): 155–159
4. Rogers ES et al. Efficacy and safety of a single dose of dexamethasone pre DOCEtaxel treatment: The Auckland experience. Annals of Oncology (2014) 25 (suppl_4): iv517-iv541
5. Fatal Neutropenic Enterocolitis With DOCEtaxel in France by Aude Lecrubier. Available at http://www.medscape.com/viewarticle/876014
6. Taxotere® Summary of Product Characteristics. Accessed May 2017. Available at :http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000073/WC500035264.pdf
7. Endoxana® Summary of Product Characteristics. Accessed May 2017. Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0167-134-004_29092016170150.pdf

Version	Date	Amendment	Approved By
1	29/04/2015		Dr Maccon Keane
2	30/05/2015	Modification of premedication regimen	Dr Maccon Keane
3	28/06/2017	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	Prof Maccon Keane
4	16/01/2019	Updated dose modification of docetaxel in hepatic impairment table Standardised administration of docetaxel and cyclophosphamide	Prof Maccon Keane
5	06/11/2019	Update of route of administration for cyclophosphamide.	Prof Maccon Keane
6	08/01/2020	Update of cyclophosphamide dose modifications in hepatic impairment	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] 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/