Dose Dense DOXOrubicin, Cyclophosphamide (AC 60/600) 14 day followed by PACLitaxel (80) 7 day Therapy (DD AC-T)

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Adjuvant Treatment of High Risk Node Negative or Node Positive Breast Cancer.	C50	00485a	Hospital
Neoadjuvant Treatment of High Risk Node Negative or Node Positive Breast Cancer.	C50	00485b	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.

Dose dense DOXOrubicin and cyclophosphamide are administered once every 14 days for four cycles (one cycle = 14 days) followed by PACLitaxel once every 7 days for 12 weeks to start **14 days after** final cycle of dose dense DOXOrubicin and cyclophosphamide.
G-CSF support (using standard or pegylated form) is required with all cycles of dose dense DOXOrubicin and cyclophosphamide.
Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Cycle 1-4 (Dose Dense):

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	DOXOrubicin	60mg/ m^2	IV push	N/A	Every 14 days for 4 cycles
2	1	Cyclophosphamide	600mg/m^2	IV infusion*	250ml 0.9% sodium chloride over 30 min	Every 14 days for 4 cycles
* Cyclophosphamide may also be administered as an IV bolus over 5-10mins						
Lifetime cumulative dose of DOXOrubicin is 450mg/m^2 **In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors outlined below[i] and to the age of the patient.**						

Cycle 5-8

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1, 8 and 15	PACLitaxel	80mg/m^2	IV infusion	250ml 0.9% sodium chloride over 1hr	Every 21 days for cycle 5-8
PACLitaxel must be supplied in non-PVC containers and administered using non-PVC giving sets and through an in-line 0.22 µm filter with a microporous membrane.					
PACLitaxel should be diluted to a concentration of 0.3-1.2mg/ml.					

ELIGIBILTY:

- Indications as above.
- ECOG status 0-2.

EXCLUSIONS:

- Hypersensitivity to DOXOrubicin, cyclophosphamide, PACLitaxel or any of the excipients.
- Congestive heart failure (LVEF < 50%) or other significant heart disease.
- Baseline neutrophil count < 1.5 x 10^9/L
- Severe hepatic impairment
- Breast feeding

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile.
- ECG
- MUGA or ECHO (LVEF > 50% to administer DOXOrubicin) if >65 years or if clinically indicated

Regular tests:

- FBC, renal and liver profile prior to each cycle
- If clinically indicated creatinine, MUGA scan or echocardiogram.

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 cycles of DOXOrubicin and Cyclophosphamide only

ANC (x10^9/L)		Platelets (x10^9/L)	Dose (All Drugs)
≥ 1	And	≥ 100	100%
<1	And	≥100	Delay for 1 week (or longer if needed), then give 100% dose if ANC > 1 and platelets ≥ 100.
≥ 1	and	< 100	Delay for 1 week (or longer if needed), then give 100% dose if ANC > 1.0 and platelets ≥ 100. Dose reduce to 75% after a second delay.
Febrile Neutropenia: 75% of dose for current and subsequent cycles.			

Table 2: Dose modifications for PACLitaxel for haematological toxicity

ANC (x10^9/L)		Platelets	Dose	Dose after neutropenic sepsis
≥ 1.5	and	> 90	80mg/m^2	65mg/m^2
*1-1.49	or	70-90	65mg/m^2	50mg/m^2
< 1	or	< 70	Delay and reduce next dose to 65mg/m^2 or add G-CSF	Delay
Patients who cannot tolerate treatment after 2 dose reductions or require a treatment delay of greater than 2 weeks, should discontinue treatment.				

*** If ANC 1 to less than 1.5 and patient fit and well can consider full dose of 80 mg/m^2 at discretion of prescribing Consultant**

Renal and Hepatic Impairment:

Table 3: Dose modification of DOXOrubicin, Cyclophosphamide and PACLitaxel in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
DOXOrubicin	No dose reduction required. Clinical decision in severe impairment		**Serum Bilirubin (micromol/L)**	**Dose**
			20-51	50%
			51-85	25%
			>85	Omit
			If AST 2-3 x normal give 75% If AST > 3 x ULN give 50%	
Cyclophosphamide	**CrCl (mL/min)**	**Dose**	Severe impairment: Clinical Decision	
	>20	100%		
	10-20	75%		
	<10	50%		
PACLitaxel	No dose reductions necessary		See Table 4 below	

Table 4: Dose modification of PACLitaxel in hepatic Impairment

ALT		Total bilirubin	Dose of PACLitaxel
< 10xULN	and	≤ 1.25xULN	80mg/m^2
< 10xULN	and	1.26-2xULN	60mg/m^2
< 10xULN	and	2.01-5xULN	40mg/m^2
≥10xULN	and/or	>5xULN	Not recommended

Non-Haematological Toxicity:

Table 5: Dose modification schedule for PACLitaxel based on adverse events

Adverse reactions	Recommended dose modification
Grade 2 motor or sensory neuropathy	Decrease dose by 10mg/m^2.
All other grade 2 non-haematological toxicity	Hold treatment until toxicity resolves to ≤ grade 1. Decrease subsequent doses by 10mg/m^2.
≥ Grade 3 reaction	Discontinue

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Dose dense DOXOrubicin cyclophosphamide cycles: High **(Refer to local policy).**
PACLitaxel: Low **(Refer to local policy)**

PREMEDICATIONS:

Dose dense DOXOrubicin cyclophosphamide cycles: None usually required (See other supportive care for g-csf support)

PACLitaxel cycles: All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to PACLitaxel treatment. Table 6 outlines suggested premedications prior to treatment with PACLitaxel.

Table 6: Suggested premedications prior to treatment with PACLitaxel

Drug	Dose	Administration prior to PACLitaxel
Dexamethasone	10mg IV[a,b]	30 minutes
Chlorphenamine	10mg IV	30 minutes
RaNITIdine[c]	50mg IV	30 minutes
[a]Dose of dexamethasone may be reduced or omitted in the absence of hypersensitivity reaction according to consultant guidance.		
[b]Dose of dexamethasone may be altered in the event of hypersensitivity reaction to 20 mg of dexamethasone orally 12 and 6 hr prior to re-challenge with PACLitaxel according to consultant guidance.		
[c]or equivalent e.g. cimetidine		

OTHER SUPPORTIVE CARE:

G-CSF (**Refer to local policy**)
Patients should have an increased fluid intake of 2-3 litres on day 1 to prevent haemorrhagic cystitis associated with cyclophosphamide.
Myalgias and arthralgias may occur with PACLitaxel. Analgesic cover should be considered.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.
Please refer to NCCP regimen 00252 for detailed information on the adverse effects associated with DOXOrubicin cyclophosphamide therapy and NCCP regimen 00226 for information relating to weekly PACLitaxel therapy

DRUG INTERACTIONS:

- CYP3A inhibitors decrease the conversion of cyclophosphamide to both its active and inactive metabolites. Patients should also be counselled with regard to consumption of grapefruit juice.
- CYP3A inducers may also increase the conversion of cyclophosphamide to both its active and inactive metabolites.
- Concurrent administration of calcium channel blockers with DOXOrubicin should be avoided as they may decrease the clearance of DOXOrubicin.
- Risk of drug interactions causing increased concentrations of PACLitaxel with CYP3A inhibitors. Patients should also be counselled with regard to consumption of grapefruit juice.
- Risk of drug interactions causing decreased concentrations of PACLitaxel with CYP3A inducers.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

DOXOrubicin	L01DB01
Cyclophosphamide	L01AA01
PACLitaxel	L01CD01

REFERENCES:

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3. Morris PG, Dickler M et al. Dose-Dense Adjuvant Doxorubicin and Cyclophosphamide Is Not Associated With Frequent Short-Term Changes in Left Ventricular Ejection Fraction. J Clin Oncol 2009;27 (36):6117-6123.
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Version	Date	Amendment	Approved By
1	01/06/2018		Prof Maccon Keane
2	23/10/2019	Standardisation of treatment table and table for suggested premedications prior to treatment with PACLitaxel	Prof Maccon Keane
3	31/12/2019	Updated recommendation for hepatic impairment	Prof Maccon Keane
4	27/05/2020	Regimen reviewed	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[ii]Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects.
Risk factors for developing anthracycline-induced cardiotoxicity include:
• high cumulative dose, previous therapy with other anthracyclines or anthracenediones
• prior or concomitant radiotherapy to the mediastinal/pericardial area
• pre-existing heart disease
• concomitant use of other potentially cardiotoxic drugs
In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient