DOXOrubicin, Cyclophosphamide (AC 60/600) 21 day followed by weekly PACLitaxel (80) Therapy (AC-T)

Note: There is an option for

- **Dose Dense DOXOrubicin, Cyclophosphamide (AC 60/600) 14 day followed by PACLitaxel (175) 14 day Therapy (DD AC-T) described in regimen NCCP- 00278.**
- **Dose Dense DOXOrubicin, Cyclophosphamide (AC 60/600) 14 day followed by PACLitaxel (80) 7 day Therapy (DD AC-T) described in regimen NCCP-00485**

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Neoadjuvant or Adjuvant Treatment of High Risk Node Negative or Node Positive Breast Cancer.	C50	00260a	DOXOrubicin: Hospital Cyclophosphamide: Hospital PACLitaxel: 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 patient's individual clinical circumstances.

DOXOrubicin and cyclophosphamide are administered once every 21 days for four cycles (one cycle = 21 days) followed by PACLitaxel administered on day 1, 8 and 15 every 21 days for 4 cycles (one cycle = 21 days) unless disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Order of Admin.	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	DOXOrubicin	60mg/ m^2	IV push	Slow IV push over 15 minutes	1-4
2	1	Cyclophosphamide	600mg/m^2	IV infusion*	250ml 0.9% sodium chloride over 30 minutes	1-4
* 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.**						

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1,8,15.	[a,b] PACLitaxel	80mg/m^2	IV infusion	250ml 0. 9% sodium chloride over 60 minutes	1-4
[a]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.					
[b]PACLitaxel should be diluted to a concentration of 0.3-1.2mg/ml.					

ELIGIBILITY:

- 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
- 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: Recommended dose modifications for cycles of DOXOrubicin and cyclophosphamide only

ANC (x10^9/L)	Platelets (x10^9/L)	Dose (Both Drugs)
≥ 1.5	≥ 90	100%
1 -1.49	70 to 90	*75%
< 1	< 70	Delay

*May consider using G-CSF for neutrophil support rather than dose reduction

Table 2: Recommended dose modifications for cycles of PACLitaxel only

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

*** 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: Recommended 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**	Dose reduction may need to be considered in severe hepatic impairment. Clinical decision			
	>20	100 %				
	10-20	75 %				
	<10	50 %				
PACLitaxel	No dose reductions necessary		**ALT**		**Total bilirubin**	**Dose**
			< 10 x ULN	and	≤ 1.25 x ULN	80 mg/m^2
			< 10 x ULN	and	1.26-2 x ULN	60 mg/m^2
			< 10 x ULN	and	2.01-5 x ULN	40 mg/m^2
			≥ 10 x ULN	and/or	> 5 x ULN	Not recommended

Non-Haematological Toxicity:

Table 4: Recommended dose modification schedule for PACLitaxel based on adverse events

Adverse reactions	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:

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

PREMEDICATIONS:

DOXOrubicin cyclophosphamide cycles: None usually required

- All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to first dose of PACLitaxel treatment.
- The H_2 antagonist, famotidine, can potentially be omitted from the pre-medication requirements for PACLitaxel but the risk of hypersensitivity with this approach is unknown.
    - Caution is advised particularly for patients receiving PACLitaxel every 3 weeks. It is recommended that if famotidine is omitted that patients are monitored closely for any signs of hypersensitivity. Any hypersensitivity should be managed as per local policy.

- Where a patient experiences hypersensitivity, consider the use of alternative H_2 antagonists **(Refer to local policy).**

Table 5 outlines suggested premedications prior to treatment with PACLitaxel.

Day of treatment	Drug	Dose	Administration prior to PACLitaxel
Day 1	Dexamethasone[a]	8mg IV	30 minutes
Day 1	Chlorphenamine	10mg IV	30 minutes
Day 1	Famotidine	20mg IV	30 minutes
Day 8[b] and thereafter	Dexamethasone[a]	None	
Day 8 and thereafter	Chlorphenamine	10mg IV	30 minutes
Day 8 and thereafter	Famotidine[c]	20mg IV	30 minutes
[a]Dose of dexamethasone may be altered, in the event of hypersensitivity reaction, to 20 mg of dexamethasone orally 12 hr and 6 hr prior to re-challenge with PACLitaxel according to consultant guidance.			
[b]Dose of dexamethasone may be added from day 8 if increased risk or previous hypersensitivity reaction according to consultant guidance.			
[c]Dose of famotidine may be omitted in the absence of hypersensitivity reaction according to consultant guidance.			

OTHER SUPPORTIVE CARE:

Prophylactic G-CSF may be used to mitigate the risk of haematological toxicities.
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 DOXOrubicin, and Cyclophosphamide (AC 60/600) Therapy -21 day** and **NCCP regimen 00226 PACLitaxel monotherapy 80mg/m^2** for information on the adverse effects/regimen specific complications.

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.

REFERENCES:

1. Citron ML, Berry DA, Cirrincione C. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003; 21 (8): 1431-1439.
2. Sparano JA, Wang M, Martino S et al. Weekly Paclitaxel in the Adjuvant Treatment of Breast Cancer: Results of Intergroup Trial E1199. N Engl J Med. 2008 April 17; 358(16): 1663-1671.
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V4 2022. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
4. DOXOrubicin 2 mg/ml concentrate for solution for infusion. Summary of Product Characteristics. Accessed Nov 2022. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-083-001_26022020112618.pdf
5. Endoxana Injection 500mg Powder for Solution for Injection. Summary of Product Characteristics Accessed Nov 2022. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2299-027-001_21122018112107.pdf
6. PACLitaxel. Summary of Product Characteristics. Accessed November 2022. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-050-001_21092022103217.pdf

Version	Date	Amendment	Approved By
1	29/04/2015		Dr Maccon Keane
2	14/06/2017	Updated title, clarified administration order and dosing in renal and hepatic impairment, applies new NCCP regimen template	Prof Maccon Keane
3	16/03/2018	Treatment table updated for standardisation. Clarified dosing of PACLitaxel in haematological toxicity	Prof Maccon Keane
4	24/09/2019	Clarified treatment cycle details Standardisation of administration times for pre-medications for PACLitaxel	Prof Maccon Keane
5	11/03/2020	Inclusion of neoadjuvant indication, standardisation of cyclophosphamide infusion volume and recommendations in hepatic impairment, standardisation of pre-medications for PACLitaxel.	Prof Maccon Keane
6	17/04/2023	Updated suggested PACLItaxel pre medications section and table.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i]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