Dose Dense DOXOrubicin, Cyclophosphamide (AC 60/600) 14 day followed by weekly PACLitaxel (80) and Trastuzumab 21 day Therapy (DD AC-TH)

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Adjuvant Treatment of HER2 positive, High Risk Node Negative or Node Positive Breast Cancer.	C50	00745a	Hospital
Neoadjuvant Treatment of HER2 positive, High Risk Node Negative or Node Positive Breast Cancer.	C50	00745b	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.

DOXOrubicin and cyclophosphamide are administered once every 14 days for four cycles (one cycle = **14 days**) followed by PACLitaxel on days 1, 8 and 15 and trastuzumab on day 1 of a **21 day** cycle for 4 cycles to start **14 days after** final cycle of DOXOrubicin and cyclophosphamide. Following completion of the 4 cycles, trastuzumab 6mg/kg (ref NCCP regimen 00200 Trastuzumab monotherapy-21days) every 21 days to complete one year of trastuzumab therapy may be given.

G-CSF support (using standard or pegylated form) is required with all cycles of doxorubicin and cyclophosphamide.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Cycle 1-4:

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	DOXOrubicin	60mg/m^2	IV push	Slow IV push over 15 minutes	Every 14 days for 4 cycles
2	1	Cyclophosphamide	600mg/m^2	IV infusion*	250ml 0.9% sodium chloride over 30min	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, 15	[a, b] PACLitaxel	80mg/m^2	IV infusion	250ml 0.9% sodium chloride over 1hr	Every 21 days for cycles 5-8
1	[c, d] Trastuzumab	8mg/kg	IV infusion Observe post infusion	250ml 0.9% sodium chloride over 90min	Cycle 5 only
1	[c, d] Trastuzumab	6mg/kg	IV infusion Observe post infusion	If no adverse reactions use 250ml 0.9% sodium chloride over 30min	Cycles 6-8
[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.					
[c]Recommended Observation period: Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms . Any deviation should be noted in local policies					
[d] Trastuzumab is incompatible with glucose solution					

ELIGIBILITY:

- Indications as above
- HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay
- 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 and TRASTUZUMAB) Regular tests:
- FBC, renal and liver profile prior to each cycle
- Cardiac function (MUGA or ECHO) every 12 weeks. Where there are signs of cardiac impairment four to eight weekly checks may be more appropriate

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.
- None usually recommended for trastuzumab. Discontinue if unacceptable toxicity occurs.
- If the patient misses a dose of trastuzumab by one week or less, then the usual maintenance dose of 6 mg/kg should be given as soon as possible. Do not wait until the next planned cycle. Subsequent maintenance doses should then be given according to the previous schedule.
- If the patient misses a dose of trastuzumab by more than one week, a re-loading dose of trastuzumab (8 mg/kg) should be given over approximately 90 minutes, at the discretion of the clinician. Subsequent trastuzumab maintenance doses (6 mg/kg) should then be given every 3 weeks from that point.

Haematological:

Table 1: Dose modifications for haematological toxicity

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.			

Renal and Hepatic Impairment:

Table 2: 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 3 below	
Trastuzumab	Probably no dose reduction necessary		Probably no dose reduction necessary	

Table 3: Dose modification of PACLitaxel in hepatic impairment

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

Non-Haematological Toxicity:

Table 4: Dose modification schedule for PACLitaxel based on adverse events

Adverse reactions	Recommended dose modification
Grade 2 motor or sensory neuropathy	Dose reduction or delay in treatment may be required.
≥ Grade 3 reaction	Discontinue

Table 5: Trastuzumab dose modification schedule based on adverse events

Adverse reactions	Recommended dose modification
LVEF drops 10 ejection fraction points from baseline and to below 50%	Withhold treatment. Repeat LVEF after 3 weeks. No improvement or further decline, consider discontinuation. Discuss with consultant and refer to cardiologist.
Symptomatic heart failure	Consider discontinuation – refer to cardiology for review. Clinical decision.

NCI-CTCAE Grade 4 hypersensitivity reactions	Discontinue
Haematological	Treatment may continue during periods of reversible, chemotherapy-induced myelosuppression. Monitor carefully for any complications of neutropenia.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

PREMEDICATIONS:

DOXOrubicin cyclophosphamide cycles: None usually required

PACLitaxel cycles:

- 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 6: 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:

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
- NCCP regimen 00226 for information relating to weekly PACLitaxel therapy
- NCCP regimen 00201 for information relating to trastuzumab 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.

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. Morris PG 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 Dec 20;27(36):6117-23. doi: 10.1200/JCO.2008.20.2952. Epub 2009 Nov 9.
3. Morris PG et al. Long-term cardiac safety and outcomes of dose-dense doxorubicin and cyclophosphamide followed by paclitaxel and trastuzumab with and without lapatinib in patients

with early breast cancer. Cancer. 2013 Nov 15;119(22):3943-51. doi: 10.1002/cncr.28284. Epub 2013 Aug 26
4. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
5. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
6. 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
7. DOXOrubicin HCl 50mg Powder for Solution for Injection. Summary of Product Characteristics. Accessed November 2022. Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0437-026-002_03032016152104.pdf
8. Cyclophosphamide (Endoxana®) Injection 500mg Powder for Solution for Injection. Accessed November 2022. Summary of Product Characteristics Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2299-027-002_21122018112109.pdf
9. PACLitaxel. Summary of Product Characteristics. Accessed November 2022. Available http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0585-029-001_17122008223616.pdf
10. Trastuzumab (Herceptin®) Summary of Product Characteristics Accessed November 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/herceptin-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	20/12/2022		Prof Patrick Morris

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