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	HSE approved reimbursement status*
Adjuvant Treatment of HER2 positive, High Risk Node Negative or Node Positive Breast Cancer.	C50	00745a	N/A
Neoadjuvant Treatment of HER2 positive, High Risk Node Negative or Node Positive Breast Cancer.	C50	00745b	N/A

*This is for post 2012 indications

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 dose dense DOXOrubicin and cycloPHOSphamide.

Facilities to treat anaphylaxis MUST be present when the systemic anti-cancer therapy (SACT) 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 NaCl 0.9% over 30 minutes	Every 14 days for 4 cycles
* cycloPHOSphamide may also be administered as an IV bolus over 5-10 minutes.						
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 NaCl 0.9% over 1 hour	Every 21 days for cycles 5-8
1	[c, d] Trastuzumab	8mg/kg	IV infusion Observe post infusion	250mL NaCl 0.9% over 90 minutes	Cycle 5 only
1	[c, d] Trastuzumab	6mg/kg	IV infusion Observe post infusion	If no adverse reactions use 250mL NaCl 0.9% over 30 minutes	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. Please see *Recommendations on Reporting on HER2 Status in Breast Cancer Patients* - Available on the NCCP website .
- 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
- Pregnancy
- 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 6mg/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 (8mg/kg) should be given over approximately 90 minutes, at the discretion of the clinician. Subsequent trastuzumab maintenance doses (6mg/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, PACLitaxel and trastuzumab in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
DOXOrubicin[a]	**CrCl (mL/min)**	**Dose**	**Serum Bilirubin (micromol/L)**	**Dose**
	> 10	No dose adjustment is needed	20-50	50% of the original dose
	< 10	No need for dose adjustment is expected	51-86	25% of the original dose
	Haemodialysis	75% of the original dose may be considered	>86 or Child-Pugh C	Not recommended
cycloPHOSphamide[b]	**CrCl (mL/min)**	**Dose**	**Level**	**Dose**
	≥30	No dose adjustment is needed	Mild and moderate	No need for dose adjustment is expected.
	10-29	Consider 75% of the original dose	Severe	Not recommended, due to risk of reduced efficacy
	<10	Not recommended, if unavoidable consider 50% of the original dose		
	Haemodialysis	Not recommended, if unavoidable consider 50% of the original dose		
PACLitaxel[c]	No need for dose adjustment is expected Haemodialysis: no need for dose adjustment is expected		See Table 3 below	
Trastuzumab[d]	**CrCl (mL/min)**	**Dose**	No need for dose adjustment is expected	
	≥ 30	No dose adjustment is needed		
	< 30	No need for dose adjustment is expected		
	Haemodialysis	No need for dose adjustment is expected		

[a] DOXOrubicin (renal and hepatic - Giraud et al 2023);
[b] cycloPHOSphamide (renal and hepatic - Giraud et al 2023);
[c] PACLitaxel (renal and hepatic – Giraud et al 2023);
[d] Trastuzumab (renal and hepatic - Giraud et al 2023).

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 – 2 x ULN	60mg/m^2
< 10 x ULN	and	2.01 – 5 x ULN	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:

As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting - Available on the NCCP website

DOXOrubicin and cycloPHOSphamide cycles: High **(Refer to local policy)**
PACLitaxel: Low **(Refer to local policy)**
Trastuzumab: Minimal **(Refer to local policy)**

For information:
Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

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 hour and 6 hour 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:

- Please refer to the relevant Summary of Product Characteristics for details.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

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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. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
5. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V6 2025. 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
6. DOXOrubicin 2mg/mL Concentrate for Solution for Infusion. Summary of Product Characteristics. Accessed February 2024. Last updated February. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-083-001_20022024123027.pdf
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Version	Date	Amendment	Approved By
1	20/12/2022		Prof Patrick Morris
2	25/04/2024	Reviewed. Updated Eligibility- HER2 Reporting. Updated exclusions- pregnancy. Dose modifications for renal and hepatic impairment updated in line with recommendations by Giraud et al 2023.	Prof Patrick Morris
2a	22/04/2025	Regimen updated in line with NCCP standardisation.	NCCP

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