CARBOplatin (AUC6) and Weekly PACLitaxel 80mg/m^2 followed by Dose Dense DOXorubicin Cyclophosphamide Therapy-Triple Negative Breast Cancer Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
Neoadjuvant treatment of triple negative breast carcinoma	C50	00348a	Hospital

**If the reimbursement status is not defined [i], 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.

CARBOplatin is administered on day 1 and PACLitaxel is administered on day 1, 8 and 15 of a 21 day cycle for 4 cycles or until disease progression or unacceptable toxicity develops.
This is then followed by 4 cycles of doxorubicin and cyclophosphamide administered once every 14 days for four cycles (one cycle = 14days)

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

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

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1, 8 and 15	PACLitaxel	80mg/m^2	IV infusion	250ml 0.9% NaCL over 1 hour	1-4
2	1	CARBOplatin	AUC 6	IV infusion	500ml glucose 5% over 60 min	1-4
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.						

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	DOXOrubicin	60mg/ m^2	IV push	N/A	5-8
2	1	Cyclophosphamide	600mg/m^2	IV infusion*	250ml 0.9% sodium chloride over 30minutes	5-8
* 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[ii] and to the age of the patient.**						

CARBOplatin dose:

The dose in mg of CARBOplatin to be administered is calculated as follows:

(mg) = target AUC (mg/ml x min) x (GFR ml/min +25)

- **Measured GFR** (e.g. nuclear renogram) is preferred whenever feasible.
- **Estimation of GFR (eGFR)** can be done by using the Wright formula or using the Cockroft and Gault formula to measure creatinine clearance.
- The GFR used to calculate the AUC dosing should not exceed 125ml/min.
- For obese and anorexic patients the formulae may not give accurate results and measured GFR is recommended. Where obesity or overweight is likely to lead to an overestimate of GFR and isotope GFR is not available the use of the adjusted ideal body weight for Cockroft and Gault may be considered (3).

WRIGHT FORMULA

There are two versions of the formula depending on how serum creatinine values are obtained, by the kinetic Jaffe method or the enzymatic method. The formula can be further adapted if covariant creatine kinase (CK) values are available (not shown).

1. *SCr measured using enzymatic assay.*

$$\text{GFR (ml/min)} = \frac{(6230 - 32.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.23 \times \text{Sex})}{\text{SCr (µmol/min)}}$$

2. *SCr measured using Jaffe assay*

$$\text{GFR (ml/min)} = \frac{(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \textit{Sex})}{\text{SCr (µmol/min)}}$$

Key: Sex = 1 if female, 0 if male; Age in years; BSA= DuBois BSA

COCKCROFT-GAULT FORMULA

$$\text{GFR (ml/min)} = \frac{S \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

S= 1.04 for females and 1.23 for males

ELIGIBILTY:

- Indications as above
- Triple negative breast cancer
- ECOG status 0-2
- Adequate organ function; ANC > 1.5 x10^9 cells/L, platelets 75 x10^9/L

EXCLUSIONS:

- Hypersensitivity to CARBOplatin*, PACLitaxel, DOXorubicin, cyclophosphamide or any of the excipients
- Congestive heart failure (LVEF < 50%) or other significant heart disease
- Disease progression while receiving platinum based chemotherapy
- Pregnancy or lactation
- Severe hepatic impairment (PACLitaxel)
- Baseline neutrophil count < 1.5 x 10^9 cells/L
- **If it is felt that the patient may have a major clinical benefit from CARBOplatin, it may in exceptional circumstances be feasible to rechallenge a patient with a prior mild hypersensitivity reaction e.g using a desensitisation protocol, but only with immunology advice, premedication as advised, and a desensitisation protocol under carefully controlled conditions with resuscitation facilities available and medical and/or ITU/ HDU supervision (2).*

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, liver and kidney profile
- Audiometry and creatinine clearance as clinically indicated.
- ECG
- MUGA or ECHO (LVEF > 50% to administer doxorubicin) if >65 years or if clinically indicated (eg smoking history, hypertension).

Regular tests:

- FBC weekly during treatment
- Liver and kidney profiles weekly
- Assessment of peripheral neuropathy status before each cycle (PACLitaxel only)
- 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:

	Dose Level	Dose Level -1	Dose Level -2
PACLitaxel	80mg/m^2	70mg/m^2	60mg/m^2
CARBOplatin	AUC 6	AUC 5	AUC 4

Haematological:

Table 1: Dose modification of CARBOplatin and PACLitaxel in haematological toxicity (CYCLE 1-4)

ANC (x10^9/L)		Platelets (x10^9/L)	CARBOplatin Dose	PACLitaxel Dose
> 1	and	≥ 75	100% Dose	100% Dose
0.5 to 0.99	and/or	<75	Delay treatment until recovery [a]	Delay treatment until recovery [a]
<0.5	and/or	<50		Omit day 8 and day 15 PACLitaxel dose
Febrile Neutropenia			Decrease CARBOplatin dose by one dose level	
<0.5 for ≥ 7 days	or	<10		
		10 to 50 with bleeding tendencies		
Treatment delay for haematological toxicity > 1 week 1st occurrence			Decrease CARBOplatin dose by one dose level to AUC 5	
2nd occurrence			Decrease CARBOplatin dose further for subsequent cycles to AUC 4	

[a]Treatment may be delayed for a maximum of 3 weeks.

Table 2: Dose modification of DOXOrubicin and cyclophosphamide in haematological toxicity (CYCLE 5-8)

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose (All Drugs)
≥ 1.0	and	≥ 100	100%
< 1.0	and	≥ 100	Delay for 1 week (or longer if needed), then give 100% dose if ANC > 1.0 and platelets ≥ 100.
≥ 1.0	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.

Renal and Hepatic Impairment:

Table 3: Dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
CARBOplatin	See note below[a]		No dose modification required			
PACLitaxel	No recommended dose modifications in renal impairment		**ALT**		**Total Bilirubin**	**Dose**
			< 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
Cyclophosphamide	**Creatinine Clearance (mL/min)**	**Dose**	No dose modification recommended			
	≥ 10	100%				
	< 10	75%				
DOXOrubicin	No dose modification recommended. Clinical decision ins evere impairment		**Serum Bilirubin (micromol/L)**			**Dose**
			20-50			50%
			> 51-85			25%
			>85			Omit
			If AST 2-3 x normal, give 75% dose. If AST >3x ULN, give 50% dose			

Renal dysfunction and CARBOplatin

- Patients with creatinine clearance values of < 60ml/min are at greater risk to develop myelosuppression.
- In case of GFR ≤ 20ml/min carboplatin should not be administered at all.
- Modification of dose based on renal function
  - If Cockroft & Gault or Wright formula are used, the dose should be adjusted per cycle based on a serum creatinine obtained within 48 hrs of drug administration.
  - If isotope GFR is used, the dose should remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine is higher than this, consideration should be given to re-measuring the GFR or to recalculating using Cockroft & Gault or Wright formulae taking care this does result in a dose reduction

Management of adverse events:

Table 4: Dose Modification of PACLitaxel for Adverse Events

Adverse reactions	Recommended dose modification
Grade ≥2 motor or sensory neuropathy First Occurrence Persistent Grade ≥2 or 2nd occurrence	 Decrease dose of PACLitaxel by 10mg/m^2. Decrease dose of PACLitaxel by a further 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

Patients who cannot tolerate treatment after 2 dose reductions or require a treatment delay of greater than 2 weeks, should discontinue treatment

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

CARBOplatin and PACLitaxel cycles: High, Day 1 **(Refer to local policy)**

Low, Day 8 and 15 **(Refer to local policy)**

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

PREMEDICATIONS:

All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to PACLitaxel treatment. DOXOrubicin cyclophosphamide cycles: None usually required

Table 5: Suggested premedications prior to treatment with PACLitaxel

Drug	Dose	Administration prior to PACLitaxel
Dexamethasone	10mg oral or IV[a]	30 minutes
Chlorphenamine [b]	10mg IV	30 minutes
Ranitidine	50mg IV	30 minutes
[a]Dose of dexamethasone may be reduced or omitted in the absence of hypersensitivity reaction according to consultant guidance		
[b] or an equivalent antihistamine e.g. diphenhydramine		

OTHER SUPPORTIVE CARE:

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.

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Hypersensitivity:** Reactions to CARBOplatin may develop in patients who have been previously exposed to platinum therapy. However allergic reactions have been observed upon initial exposure to CARBOplatin. Severe hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment, angioedema and generalised urticaria have occurred in <1% of patients receiving PACLitaxel after adequate premedication. In the case of severe hypersensitivity reactions, PACLitaxel infusion should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be re-challenged with the drug.
- **Neurotoxicity and ototoxicity:** Neurological evaluation and an assessment of hearing should be performed on a regular basis, especially in patients receiving high dose CARBOplatin. Neurotoxicity, such as parasthesia, decreased deep tendon reflexes, and ototoxicity are more likely seen in patients previously treated with cisplatin, other platinum treatments and other ototoxic agents. Frequency of neurologic toxicity is also increased in patients older than 65 years.
- **Peripheral neuropathy**: Occurs frequently but the development of severe symptoms is rare. In severe cases, a dose reduction may be considered for all subsequent courses of PACLitaxel as per consultant guidance.
- **Arthralgia/myalgia**: May be severe in some patients; however, there is no consistent correlation between cumulative dose and infusion duration of PACLitaxel and frequency or severity of the arthralgia/myalgia. Symptoms are usually transient, occurring within 2 or 3 days after PACLitaxel administration, and resolving within days. Dose reducing PACLitaxel may lessen the severity of arthralgias/myalgias; however, there is no data on efficacy of reduced doses in a curative setting. Dose reduction should be considered only if symptom severity precludes continuing PACLitaxel.
- **Extravasation**: PACLitaxel causes pain and tissue necrosis if extravasated. DOXOrubicin may cause pain and tissue necrosis if extravasated. **(Refer to local policy).**
- **Hepatic Dysfunction**: Patients with hepatic impairment may be at increased risk of toxicity, particularly grade 3-4 myelosuppression.
- **Cardiac conduction abnormalities:** If patients develop significant conduction abnormalities during PACLitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with PACLitaxel. Hypotension, hypertension, and bradycardia have been observed during PACLitaxel administration; patients are usually asymptomatic and generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of PACLitaxel infusion, is recommended.
- **Cardiac Toxicity**: DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction.
- **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:

- Avoid concurrent use with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.

- Avoid concurrent use with ototoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS). When necessary perform regular audiometric testing
- Risk of drug interactions causing increased concentrations of PACLitaxel with CYP3A inhibitors.
- Risk of drug interactions causing decreased concentrations of PACLitaxel with CYP3A inducers.
- 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.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

CARBOplatin	L01XA02
PACLitaxel	L01CD01
Doxorubicin	L01DB01
Cyclophosphamide	L01AA01

REFERENCES:

1. Impact of the addition of carboplatin and or bevacizumab to neoadjuvant once per week paclitaxelfollowed by dose dense AC on pathologic complete response rates in stage II to III TNBC: CALGB 40603 (alliance) Sikov et al. J Clin Oncol. 2015 Jan 1; 33(1): 13–21.
2. NCCN Guidelines Version1.2015 Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer
3. Appropriate chemotherapy dosing for obese adult patients with cancer:American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2012; 30 (13) 1553-1561.
4. CARBOplatin Summary of Product Characteristics Accessed January 2016. Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0749-004-001_19062014145041.pdf
5. PACLitaxel. Summary of Product Characteristics. Accessed January 2016. Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1426-002-001_01072015115039.pdf

Version	Date	Amendment	Approved By
1	01/12/2016		Prof Maccon Keane
2	26/11/2018	Updated to new NCCP template. Standardisation of • administration volumes and fluids , • dosing in renal and hepatic impairment • premedications Updated emetogenic status of CARBOplatin	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/

[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