CARBOplatin (AUC6) and Weekly PACLitaxel 80mg/m^{2}Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Adjuvant treatment of high risk, stage I, epithelial ovarian cancer[i]	C56	00308a	Hospital
Treatment of advanced ovarian cancer	C56	00308b	Hospital
Treatment of primary peritoneal cancer	C48	00308c	Hospital
Treatment of fallopian tube cancer	C57	00308d	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.

Adjuvant treatment:
CARBOplatin is administered on Day 1 and PACLitaxel is administered weekly on Day 1, 8 and 15 of a **21 day** cycle for 3-6 cycles or until disease progression or unacceptable toxicity develops.

Advanced ovarian, primary peritoneal and fallopian tube cancer:
CARBOplatin is administered on Day 1 and PACLitaxel is administered weekly on day 1, 8 and 15 of a **21 day** cycle for 6 cycles or until disease progression or unacceptable toxicity develops.

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 60min	Every 7 days for 3-6 cycles as indicated
2	1	CARBOplatin	AUC 6	IV infusion	500ml glucose 5% over 60 min	Every 21 days for 3-6 cycles as indicated
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.						

CARBOplatin dose:

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

Dose (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*.

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

2. *SCr measured using Jaffe assay*

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

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
- Life expectancy > 3months
- ECOG status 0-3*

**For otherwise fit patients being treated in the neo-adjuvant setting or in the adjuvant setting with the aim of long-term disease control, these protocol doses may be appropriate despite a PS of 3, where a PS of 3 is attributable to disease burden or recent events*

EXCLUSIONS:

- Hypersensitivity to CARBOplatin**, PACLitaxel or any of the excipients.
- 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 (5).

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Audiometry and creatinine clearance as clinically indicated

Regular tests:

- FBC with differential, renal and liver profile weekly during treatment
- Assessment of peripheral neuropathy before each cycle

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.

DRUG	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 modifications for haematological toxicity Cycle 2-6

Day	ANC (x10^9/L)		Platelet count (x10^9/L)	CARBOplatin Dose	PACLitaxel Dose
Day 1	≥1	and	≥75	100% Dose	100% Dose
	<1	and/or	<75	Delay treatment until recovery [a]	Delay treatment until recovery [a]
Day 8, 15	<0.5	and/or	<50		Omit day 8 and day 15 PACLitaxel dose
Day 1	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.

Renal and hepatic impairment

Table 2: Dose Modification of CARBOplatin and PACLitaxel in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment			
CARBOplatin	See note below[b]	No dose modification required			
PACLitaxel	No dose modification required	**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

[b]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.
- 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 remeasuring 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 3: Dose Modifications for Adverse Events

Adverse reactions	Recommended dose modification
Grade ≥ 2 Motor or sensory neuropathy First occurrence Persistent Grade ≥ 2 or second 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 3 weeks, should discontinue treatment.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Day 1 High (**Refer to local policy).**

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

PREMEDICATIONS:

All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to Paclitaxel treatment. Table 4 outlines suggested premedications prior to treatment with PACLitaxel.

Table 4: 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:

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:** This is the dose limiting toxicity. 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. Dose reduction or discontinuation may be necessary.
- **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.
- **Hepatic Dysfunction:** Patients with hepatic impairment may be at increased risk of toxicity, particularly grade 3-4 myelosuppression.
- **Extravasation**: PACLitaxel causes pain and tissue necrosis if extravasated. **(Refer to local policy).**
- **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.

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.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

CARBOplatin L01XA02
PACLitaxel L01CD01

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Version	Date	Amendment	Approved By
1	08/04/2016		Prof Maccon Keane
2	18/04/2018	Updated with new NCCP regimen template. Treatment table updated for standardization. Updated emetogenic status as per NCCN	Prof Maccon Keane
3	23/10/2019	Standardised table for suggested premedications prior to treatment with PACLitaxel	Prof Maccon Keane
4	20/11/2019	Renaming regimen and updating treatment table to exclude range of CARBOplatin dosing to facilitate inclusion of regimen in NCIS	Prof Maccon Keane
5	29/04/2020	Updated emetogenic potential and adverse events	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This regimen is outside its licensed indication in Ireland. Patients should be informed of the unlicensed nature of this indication and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be aware of their responsibility in communicating any relevant information to the patient and also in ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.