CISplatin (50mg/m^2) Chemoradiation followed by CARBOplatin (AUC 5) and PACLitaxel (175mg/m^2) – Endometrial Cancer

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Adjuvant treatment for high risk, stage I (grade 3 with deep myometrial invasion and/or lymph-vascular invasion) stage II or III endometrial carcinoma or stage I–III endometrial carcinoma with serous or clear cell histology following surgery	C54	00676a	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 is recommended to start within 4-6 weeks of surgery.

CISplatin is administered once every 21 days for 2 cycles with concurrent radiotherapy.
This is then followed by 4 cycles of PACLitaxel and CARBOplatin administered once every 21 days and is initiated within 3 weeks of completion of radiation therapy.

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

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	CISplatin	50mg/m^2	IV Infusion	1000ml NaCl 0.9% over 60 minutes (Pre and Post hydration therapy required)**	Every 21 days

**** Pre and post hydration therapy required for CISplatin**
See local hospital policy recommendations.
Suggested prehydration for CISplatin therapy:

1. Administer 10mmol magnesium sulphate ($MgSO_4$) ((+/-KCl 10-20mmol/L if indicated) in 1000 mL sodium chloride 0.9% over 60 minutes.

Administer CISplatin as described above (2).
Post hydration: Administer 1000 ml 0.9% NaCl over 60mins.
Mannitol 10% may be used to as per local policy to induce diuresis, although there is no conclusive evidence that this is required. The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload (3,4).

CISplatin (radiosensitizer) – Radiotherapy Since CISplatin is used in this regimen as a radiosensitising agent, it is to be administered on the day on which radiotherapy is delivered.
Radiotherapy should start after CISplatin infusion is completed. If radiotherapy is cancelled on the CISplatin day, do not give CISplatin that day and postpone chemotherapy until radiation therapy resumes.

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Admin. order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	PACLitaxel	175mg/m^2	IV Infusion	500ml NaCl 0.9% over 3 hours	Every 21 days
2	1	CARBOplatin	AUC 5	IV Infusion	500ml Glucose 5% over 30 minutes	Every 21 days
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 membrance						
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)** may be performed using the Wright formula to estimate GFR or the Cockcroft and Gault formula to measure creatinine clearance.
- The GFR used to calculate the AUC dosing should not exceed 125ml/min .
- For obese patients and those with a low serum creatinine, for example, due to low body weight or post-operative asthenia, estimation using formulae may not give accurate results; measured GFR is recommended.
    - where obesity (body mass index [BMI] ≥ 30 kg/m^2) or overweight (BMI 25-29.9) is likely to lead to an overestimate of GFR and isotope GFR is not available the use of the adjusted ideal body weight in the Cockcroft and Gault formula may be considered.
    - where serum creatinine is less than 63 micromol/L, the use of a creatinine value of 62 micromol/L or a steady pre-operative creatinine value may be considered

• These comments do not substitute for the clinical judgement of a physician experienced in prescription of CARBOplatin.

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*

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GFR (ml/min) = (6580 - 38.8 x Age) x BSA x (1 - 0.168 x Sex)
SCr (micromol/min)

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

COCKCROFT-GAULT FORMULA

GFR (ml/min) = S x (140 - age in years) x wt (kg)
serum creatinine (micromol/L)

S= 1.04 for females

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- Adequate hepatic, renal, and bone marrow function

EXCLUSIONS:

- Hypersensitivity to CISplatin, CARBOplatin*, PACLitaxel or any of the excipients
- Moderate/severe renal impairment (creatinine clearance < 60 mL/min)
- Significant hearing impairment/tinnitus
- Peripheral neuropathy ≥ 2
- Pregnancy or lactation

*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

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- Blood, renal and liver profile
- Audiology and creatinine clearance if clinically indicated
- Isotope GFR measurement (preferred) or GFR / Creatinine Clearance estimation

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Regular tests:

- FBC with differential, renal and liver profile 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.

Chemoradiation: CISplatin

Haematological:

Table 1: Dose modification of CISplatin in haematological toxicity

ANC (x10^9/L)		Platelets (x10^9/L)	Dose
<1.5	**or**	<100	Postpone one week. If recovery requires > 1 week stop CISplatin

Management of adverse events:

Table 2: Dose Modification of CISplatin for Adverse Events

	Adverse reactions	Recommended dose modification
CISplatin	Peripheral neuropathy Grade 2 Grade 3 or 4	 Reduce CISplatin dose by 25% Omit CISplatin

CARBOplatin and PACLitaxelHaematological:

Table 3: Dose modifications for haematological toxicity for PACLitaxel and CARBOplatin

ANC (x 10^9/L) On Treatment Day	
0.5 to < 1.0	Delay treatment until recovery
< 0.5	Delay treatment until recovery and consider reducing PACLitaxel and CARBOplatin by 25% for subsequent cycles
Febrile neutropenia	Delay treatment until recovery and consider reducing PACLitaxel and CARBOplatin by 25% for subsequent cycles
Platelets (x 10^9/L) at any stage in cycle	
50 to <100	Delay treatment until recovery
<50	Delay treatment until recovery and consider reducing PACLitaxel and CARBOplatin by 25% for subsequent cycles

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Management of adverse events:

Table 4: Dose Modification for Adverse Events

Adverse reactions	Recommended dose modification
Motor or sensory neuropathy Grade 2 Grade ≥ 3	Reduce PACLitaxel by 25% If persists, reduce PACLitaxel by 50% Omit PACLitaxel
≥ Grade 3 reaction	Discontinue

Renal and Hepatic Impairment:

Table 5: Dose modification in renal and hepatic impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal Impairment</th><th colspan="4">Hepatic Impairment</th></tr>
<tr><td rowspan="5">CISplatin</td><td>CrCl (ml/min)</td><td>Dose</td><td colspan="4" rowspan="5">No dose modifications for hepatic impairment</td></tr>
<tr><td>≥60</td><td>100%</td></tr>
<tr><td>45-59</td><td>75%</td></tr>
<tr><td colspan="2" rowspan="2"><45</td></tr>
<tr><td>Hold CISplatin or delay with additional IV fluids or go to CARBOplatin</td></tr>
<tr><td rowspan="5">PACLitaxel</td><td colspan="2" rowspan="5">No dose modification required</td><td>ALT</td><td></td><td>Total bilirubin</td><td>Dose of PACLitaxel</td></tr>
<tr><td>< 10xULN</td><td>and</td><td>≤ 1.25xULN</td><td>175mg/m^2</td></tr>
<tr><td>< 10xULN</td><td>and</td><td>1.26-2xULN</td><td>135mg/m^2</td></tr>
<tr><td>< 10xULN</td><td>and</td><td>2.01-5xULN</td><td>90mg/m^2</td></tr>
<tr><td>≥ 10xULN</td><td>and/or</td><td>> 5xULN</td><td>Not recommended</td></tr>
<tr><td>CARBOplatin</td><td colspan="2">See note below[a]</td><td colspan="4">No dose modification required</td></tr>
</table>

[a]Renal dysfunction and CARBOplatin:

- Patients with creatinine clearance values of < 60ml/min are at greater risk of developing myelosuppression.
- If GFR between 20 to ≤ 30ml/min CARBOplatin should be administered with extreme caution.
- If GFR ≤ 20ml/min, CARBOplatin should not be administered at all.
- If Cockcroft & Gault or Wright formula are used, the dose should be calculated as required on each cycle based on a serum creatinine obtained within 48 hrs of drug administration.
- If isotope GFR is used, the dose can remain the same provided the serum creatinine is ≤ 110% of its value at the time of the isotope measurement. If the serum creatinine increases, consideration should be given to re-measuring the GFR or to estimating it using Cockcroft & Gault or Wright formulae.

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SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

CISplatin: High **(Refer to local policy)**
PACLitaxel: Low **(Refer to local policy)**
CARBOplatin: High **(Refer to local policy)**

PREMEDICATIONS:

Hydration pre and post CISplatin administration **(Reference local policy or see recommendations above).**

- All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to the 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 pre-medications prior to treatment with PACLitaxel

Drug	Dose	Administration prior to PACLitaxel
dexAMETHasone	20mg oral or IV[a,b]	For oral administration: approximately 6 and 12 hours or for IV administration: 30 minutes
Chlorphenamine	10mg IV	30 minutes
Famotidine[c]	20mg IV	30 minutes
[a]Dose of dexAMETHasone may be reduced or omitted in the absence of hypersensitivity reaction according to consultant guidance.		
[b]If aprepitant is added to the anti-emetic regimen, consideration should be given to reducing the dose of dexAMETHasone to 12mg on the day of treatment.		
[c]Dose of famotidine may be omitted in the absence of hypersensitivity reaction according to consultant guidance.		

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.

CISplatin:

- **Renal toxicity:** Renal toxicity is common with CISplatin. Encourage oral hydration.
- **Ototoxicity and sensory neural damage:** This should be assessed by history prior to each cycle.

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PACLItaxel:

- **Hypersensitivity:** 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**.**
- **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.
- **Peripheral neuropathy:** Occurs frequently but the development of severe symptoms is rare. Dose reduction or discontinuation may be necessary.

CARBOplatin:

- **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 to be 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.

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.

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Version	Date	Amendment	Approved By
1	20/08/2021		Prof Maccon Keane
2	04/09/2023	Reviewed. Updated CISplatin and CARBOplatin infusion time. Updated standard wording for CARBOplatin dosing , exclusion criteria, renal dysfunction and creatinine value. Updated PACLItaxel pre medications table.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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