PACLitaxel/CISplatin alternating with PACLitaxel/Etoposide (TP/TE) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of women with high-risk Gestational Trophoblastic Neoplasia (GTN) who have not responded or have relapsed from treatment with EMA/CO.	D39	00266a	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.

Treatment with PACLitaxel and CISplatin (TP) alternates every 14 days with PACLitaxel and etoposide (TE), and is administered for 2-4 cycles (1 cycle = 28 days) until normalisation of human chorionic gonadotropin (hCG) values or unacceptable toxicity develops.
Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate
1	1	PACLitaxel	135mg/m^2	IV	500ml 0.9% NaCl over 3 hours[a]
2	1	CISplatin	60mg/m^2	IV	1000ml 0.9% NaCl over 60 mins [b]
1	15	PACLitaxel	135mg/m^2	IV	500ml 0.9% NaCl over 3 hours
2	15	Etoposide	150mg/m^2	IV	1000ml 0.9% NaCl over 60 mins[c]
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.					
[a]PACLitaxel should be diluted to a concentration of 0.3-1.2mg/ml.					
[b]**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 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).					
[c]Hypotension following rapid IV administration has been reported. Longer infusion times may be required based on the patient's tolerance					

ELIGIBILITY:

- Indications as above
- CrCl > 50ml/min

EXCLUSIONS:

- Hypersensitivity to PACLitaxel, CISplatin, etoposide or any of the excipients
- CISplatin
    - Pre-existing neuropathies ≥ grade 2
    - Creatinine clearance < 60 mL/min
    - Significant hearing impairment/tinnitus
- Severe hepatic impairment (etoposide)

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- ECG
- Serum hCG using a validated test method
- Audiology and creatinine clearance if clinically indicated

Regular tests:

- FBC, renal and liver profile
- Serum hCG (using a validated test method) should be done on day one of each cycle or more frequently if required
    - After remission is achieved, serum hCG (using a validated test method) should be measured fortnightly for six months after consolidation therapy then monthly for a further six months and then every two months for two years

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.
- In general treatment may proceed if neutrophils ≥ 1 x10^9/L and platelets > 75 x10^9/L.
- The use of G-CSF support is recommended.

Renal and Hepatic Impairment:

Table 1: Dose modifications in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
Etoposide	**CrCl (ml/min)**	**Dose**	**Bilirubin (micromol/L)**		**AST**	**Dose**
	>50	100%	26-51	or	60-180	50%
	15-50	75%	>51	or	>180	Clinical decision
	<15	50%				
	Subsequent doses should be based on clinical responses					
CISplatin	**CrCl (ml/min)**	**Dose**	No dose reduction necessary			
	50-59	50mg/m^2				
	40-49	40mg/m^2				
	<40	CARBOplatin AUC 4				
PACLitaxel	No dose reductions necessary		Dose reduction may be required. Clinical decision			

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

PREMEDICATIONS:

- 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 2: Suggested premedications 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:

Hydration prior and post CISplatin administration **(Reference local policy or see recommendations above).**
G-CSF may be used to mitigate the risk of haematological toxicities.
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. G-CSF will likely be needed to maintain white blood cell count.
- **Hypersensitivity**: There is a high risk of hypersensitivity reactions with PACLitaxel, CISplatin and etoposide.
  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.
  Monitor infusion of etoposide for the first 15 minutes for signs of hypotension.

PACLitaxel

- **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.

CISplatin

- **Renal Toxicity:** Nephrotoxicity is common with CISplatin. Encourage oral hydration. If oral hydration is not possible (e.g. excessive nausea), IV hydration is indicated. Avoid nephrotoxic drugs such as aminoglycoside antibiotics where possible. Where treatment with nephrotoxic drugs must be used, monitor renal function.
- **Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle of CISplatin.

DRUG INTERACTIONS:

- 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.
- CISplatin may potentiate the nephrotoxic and ototoxic effects of loop diuretics and aminoglycosides so concurrent use should be avoided.
- Concomitant CISplatin therapy is associated with reduced total body clearance of etoposide.
- CYP3A4 inducers may increase the clearance of etoposide.
- CYP3A4 and p-gp inhibitors may decrease the clearance of etoposide
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	01/02/2016		Prof Maccon Keane
2	22/02/2018	Clarified dosing in renal and hepatic impairment. Applied new NCCP regimen template	Prof Maccon Keane
3	22/10/2021	Reviewed. Updated CISplatin hydration and Exclusions. Updated baseline tests. Updated hCG testing (baseline and regular tests). Updated emetogenic potential. Standardised premedications. Updated adverse effects and drug interactions.	Prof Maccon Keane
4	14/04/2023	Updated suggested PACLItaxel pre medications section and table.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.