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

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

Treatment with PACLitaxel and CISplatin (TP) alternates every 14 days with PACLitaxel and etoposide (TP), and is administered for 2-4 cycles (1 cycle = 28 days) until normalisation of hCG values or unacceptable toxicity develops.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate
1	1	PACLitaxel	135mg/m^2	IV	500ml 0.9% NaCl over 3hours[a]
2	1	CISplatin	60mg/m^2	IV	1000ml 0.9% NaCl over 2 hours [b]
1	15	PACLitaxel	135mg/m^2	IV	500ml 0.9% NaCl over 3hours
2	15	Etoposide	150mg/m^2	IV	1000 ml 0.9% NaCl over 60mins[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 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 (4,5).

[c]Hypotension following rapid IV administration has been reported.
Longer infusion times may be required based on the patient's tolerance

ELIGIBILTY:

- Indications as above
- GFR > 50ml/min

EXCLUSIONS:

- Hypersensitivity to PACLitaxel, CISplatin, etoposide or any of the excipients
- Severe hepatic impairment

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- ECG
- human chorionic gonadotropin (hCG)

Regular tests:

- FBC, renal and liver profile
- hCG
- Patient should have hCG levels monitored twice weekly during treatment.
  - After remission is achieved, serum hCG should be measured fortnightly until monitoring has shown one year of normal hCG levels.
  - Follow-up for at least 5 years may be considered for those at highest risk**.**

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	**Cr Cl (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	**Cr Cl (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: High (**Refer to local policy).**

PREMEDICATIONS:

All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to PACLitaxel treatment. Table 2 outlines suggested premedications prior to treatment with PACLitaxel.

Table 2: Suggested premedications prior to treatment with PACLitaxel

Drug	Dose	Administration prior to PACLitaxel
Dexamethasone	20mg oral or IV[a]	For oral administration: approximately 6 and 12 hours or for IV administration: 30 to 60 min
Diphenhydramine [b]	50mg IV	30 to 60 minutes
Cimetidine or ranitidine	300mg IV 50mg IV	30 to 60 minutes
[a]Dose of dexamethasone may be reduced in the absence of hypersensitivity reaction according to consultant guidance		
[b] or an equivalent antihistamine e.g. chlorpheniramine		

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

OTHER SUPPORTIVE CARE:

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 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.
- **Renal Toxicity:** Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics.
- **Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle of CISplatin.
- **Extravasation**: PACLitaxel causes pain and tissue necrosis if extravasated (Refer to local policy).

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

ATC CODE:

PACLitaxel	L01CD01
Etoposide	L01CB01
CISplatin	L01XA01

REFERENCES:

1. Wang J, Short D et al Salvage Chemotherapy of relapsed or high-risk gestational trophoblastic neoplasia (GTN) with paclitaxel/cisplatin alternating with paclitaxel/etoposide (TP/TE). Annals Oncol. 2008;19: 1578-1583.
2. Osborne R, Covens A et al Successful Salvage of Relapsed High-Risk Gestational trophoblastic Neoplasia Patients using a Novel Paclitaxel-Containing Doublet. J. Reprod. Med. 2004;49(8):655-61
3. NCCP Clinical Guidelines Diagnosis, staging and treatment of patients with gestational trophoblastic disease 2015. Available at http://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/gtd/gtdguideline.pdf
4. Nephrotoxicity Associated with CISplatin EviQ ID: 184 v.3 https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/prophylaxis-and-prevention/184-nephrotoxicity-associated-with-CISplatin
5. Portilla D et al. CISplatin nephrotoxicity. UptoDate Accessed Oct 2017 https://www.uptodate.com/contents/CISplatin-nephrotoxicity?source=search_result&search=CISplatin%20hydration&selectedTitle=1~150

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

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/