EP/EMA Therapy (Etoposide CISplatin/Etoposide Methotrexate DACTINomycin)

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	00264a	Hospital
GTN and hepatic metastases Women with GTN and hepatic metastases at presentation	D39	00264b	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 etoposide and CISplatin (EP) alternates every 7 days with etoposide, methotrexate and DACTINomycin (EMA) and is administered continuously until normalization of hCG values or unacceptable toxicity develops.

Patients with high-risk disease should have maintenance therapy for 3 cycles (6 weeks) after normalisation of hCG values.

This may be extended to 4 cycles (8 weeks) in patients with poor prognostic features such as liver metastases with or without brain metastases.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Etoposide	150mg/m^2	IV	1000 ml 0.9% NaCl over 60mins[a]	See above for details
2	1	CISplatin	75mg/m^2	IV	1000ml 0.9% NaCl over 2 hours[b]	See above for details
1	8	DACTINomycin	0.5mg	IV Bolus	n/a	See above for details
2	8	Etoposide	100mg/m^2	IV	1000 ml 0.9% NaCl over 60mins	See above for details
3	8	Methotrexate	300mg/m^2	IV	1000ml 0.9% NaCl over 12 hours	See above for details
4	8 (taken day 9)	Folinic Acid	15mg	PO	Every 12 hours for 4 doses (to be started 24hrs after start of methotrexate)	See above for details

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

[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).

ELIGIBILTY:

- Indications as above

EXCLUSIONS:

- Hypersensitivity to etoposide, CISplatin, methotrexate, DACTINomycin, or any of the excipients.

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- 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.

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			
	>60	100%				
	45-59	75%				
	<45	Consider CARBOplatin				
Methotrexate	Cr Cl (ml/min)	Dose	**Bilirubin (micromol/L)**		**AST (Units)**	**Dose**
	>80	100%	<50	and	<180	100%
	60	65%	51-85	or	>180	75%
	45	50%	>85			CI
	<30	CI				
DACTINomycin	Clinical decision – unlikely to require a reduction.		Consider dose reduction in severe hepatic disease.			

Management of adverse events:

Table 2: Dose Modification of methotrexate for Adverse Events

Adverse reactions	Recommended dose modification
Mucositis	Consider doubling folinic acid both in dose and duration before considering reduction in the dose of methotrexate.
Third space fluids (ascites, pleural effusions, very large ovarian cysts)	Hold methotrexate until recovery.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: High (**Refer to local policy).**

PREMEDICATIONS:

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.

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**: Hypersensitivity reactions have been reported with etoposide and CISplatin. Monitor infusion of etoposide for the first 15 minutes for signs of hypotension.
- There is a high risk of hypersensitivity reactions with etoposide.
- **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**: DACTINomycin can cause pain and tissue necrosis if extravasated.

DRUG INTERACTIONS:

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

ATC CODE:

Etoposide	L01CB01
CISplatin	L01XA01
Methotrexate	L01BA01
DACTINomycin	L01DA01
Folinic Acid	V03AF03

REFERENCES:

1. Newlands ES, Mulholland PJ et al. Etoposide and Cisplatin/Etoposide, Methotrexate, and Actinomycin D (EMA) Chemotherapy for Patients With High-Risk Gestational Trophoblastic Tumors Refractory to EMA/Cyclophosphamide and Vincristine Chemotherapy and Patients Presenting With Metastatic Placental Site Trophoblastic Tumors J Clin Oncol 2000; 18,(4)854-859
2. May T, Goldstein DP et al. Current Chemotherapeutic Management of Patients with Gestational Trophoblastic Neoplasia Chemotherapy Research and Practice 2011;Article ID 806256,
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	20/06/2016		Prof Maccon Keane
2	07/02/2018	Updated with new NCCP regimen template, updated CISplatin hydration recommendations, clarified dosing in renal and hepatic impairment	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/