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

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

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, methotrexate and DACTINomycin (EMA) alternates every 7 days with etoposide and CISplatin (EP) and is administered continuously until normalisation of human chorionic gonadotropin (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	DACTINomycin	0.5mg	IV Bolus	n/a	See above for details
2	1	Etoposide	100mg/m^2	IV	1000ml 0.9% NaCl over 60mins[a]	See above for details
3	1	Methotrexate	300mg/m^2	IV	1000ml 0.9% NaCl over 12 hours	See above for details
4	2, 3	Folinic Acid	15mg	PO	Every 12 hours for 4 doses (to be started 24hrs after start of methotrexate)	See above for details
1	8	Etoposide	150mg/m^2	IV	1000ml 0.9% NaCl over 60mins[a]	See above for details
2	8	CISplatin	75mg/m^2	IV	1000ml 0.9% NaCl over 2 hours[b]	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 pre hydration 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 (4, 5).

ELIGIBILITY:

- 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
- 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.

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

Management of adverse events:

Table 2: Dose Modification for Adverse Events

Adverse reactions	Recommended dose modification
Peripheral neuropathy Grade 2, Grade 3 or Grade 4	Omit CISplatin
Mucositis and stomatitis or Diarrhoea **Grade 3**: 1st occurrence: 2nd occurrence: **Grade 4**: 1st occurrence: 2nd occurrence:	 Delay treatment until toxicity has resolved to Grade 1 or less and reduce doses for subsequent cycles as follows: Reduce DACTINomycin, etoposide, methotrexate, and CISplatin by 25% Reduce DACTINomycin, etoposide, methotrexate, and CISplatin by 50% Delay treatment until toxicity has resolved to Grade 1 or less and reduce doses for subsequent cycles as follows: Reduce DACTINomycin, etoposide, methotrexate, and CISplatin by 50% Cease treatment
Third space fluids (ascites, pleural effusions, very large ovarian cysts)	Hold methotrexate until recovery.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Etoposide: Low **(Refer to local policy).**
CISplatin: High **(Refer to local policy).**
DACTINomycin: Moderate **(Refer to local policy).**
Methotrexate: Moderate **(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.

CISplatin

- **Renal Toxicity:** Nephrotoxicity is common with CISplatin. Strongly 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.

DACTINomycin

- **Extravasation**: DACTINomycin can cause pain and tissue necrosis if extravasated.

Methotrexate

- **Respiratory system**: Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia may occur and deaths have been reported. Symptoms typically include dyspnoea, cough (especially a dry non-productive cough) and fever for which patients should be monitored at each follow-up visit. Patients should be informed of the risk of pneumonitis and advised to contact their doctor immediately should they develop persistent cough or dyspnoea.
- **Hepatotoxicity**: Methotrexate-induced hepatotoxicity can be seen with both high and low-dose methotrexate, and can be life-threatening. Increased serum aminotransferases and less commonly hyperbilirubinemia is seen more often in high-dose methotrexate. The liver enzymes can increase with each cycle, and usually return to pre- treatment levels once methotrexate has been discontinued for 1 month. Cirrhosis and fibrosis are more often seen with chronic low-dose methotrexate. Patients should be warned to avoid alcohol, prescription medications or herbal supplements that may increase risk of hepatotoxicity.
- **Pleural effusions and ascites**: These should be drained prior to initiation of methotrexate treatment.

DRUG INTERACTIONS:

- 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
- NSAIDs may decrease the clearance of methotrexate by decreasing its renal perfusion and tubular secretion thus increasing its toxicity.
- Sulphonamides and penicillins may displace bound methotrexate from plasma protein increasing serum methotrexate levels and its toxicity.
- Concomitant administration of drugs that cause folate deficiency may lead to increased methotrexate toxicity.
- Ciprofloxacin may inhibit renal tubular transport of methotrexate, increasing serum methotrexate levels and its toxicity.
- Probenecid may inhibit renal excretion of methotrexate, increasing serum methotrexate levels and its toxicity.
- Current drug interaction databases should be consulted for more information.

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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
3	22/10/2021	Updated title and treatment (wording and table). Updated CISplatin prehydration (KCl). Updated Baseline tests. Updated hCG testing (baseline and regular tests). Standardisation of methotrexate renal and hepatic impairment. Updated Table 2. Update of emetogenic potential. Updated adverse effects and drug interactions.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.