EMA/CO Therapy (Etoposide, Methotrexate, DACTINomycin, Cyclophosphamide, vinCRIStine)

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of high risk gestational trophoblastic neoplasia (GTN) (FIGO score ≥7)	D39	00248a	Hospital
Treatment of patients with low risk GTN who have not responded or have relapsed from sequential single-agent treatment single agent chemotherapy (methotrexate and DACTINomycin)	D39	00248b	Hospital
Treatment of patients with low-risk GTN who have not responded to methotrexate with a hCG >1,000 IU/L	D30	00248c	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 EMA (etoposide, methotrexate, DACTINomycin) alternates every week with vinCRIStine and cyclophosphamide and is administered continuously until human chorionic gonadotropin (hCG) values fall below the upper limit of normal or unacceptable toxicity develops.

Low risk GTN: Treatment should be continued until hCG is normal and then usually for three further courses to eliminate any residual tumour cells and to minimise the chances of relapse.

High risk GTN: Treatment should be continued 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.

- Etoposide can be omitted once hCG levels fall below the upper limit of normal to reduce the risk of AML/MDS.
- Steroid dosing should be minimised to reduce the risk of avascular necrosis.
- G-CSF therapy is often required to maintain dose intensity of this regimen.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1, 2	DACTINomycin	0.5mg	IV Bolus	n/a	See above for details
2	1, 2	Etoposide	100mg/m^2	IV	1000ml 0.9% NaCl over 60 mins*	See above for details
3	1	Methotrexate	300mg/m^2	IV	1000ml 0.9% NaCl over 12 hours	See above for details
1	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	**vinCRIStine	0.8mg/m^2 (cap dose at 2mg)	IV infusion	50mL 0.9% NaCl minibag over 15 minutes.	See above for details
2	8	Cyclophosphamide	600mg/m^2	IV	250ml 0.9% NaCl over 30 minutes	See above for details

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

**vinCRIStine is a neurotoxic chemotherapeutic agent.
Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer

ELIGIBILITY:

- Indications as above

EXCLUSIONS:

- Hypersensitivity to etoposide, methotrexate, folinic acid, DACTINomycin, vinCRIStine, cyclophosphamide 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

Regular tests:

- FBC, renal and liver profile prior to each cycle.
  - 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 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.
- Due to the curative aim of treatment, dose modifications should be avoided and made only made after discussion with the Consultant in charge of treatment.
- G-CSF support may be considered.
- In general treatment may proceed if neutrophils > 1.0 x10^9/L and platelets > 75 x10^9/L.
- To avoid extended intervals between courses caused by myelosuppression, it may occasionally be necessary to reduce the EMA by omitting the day 2 doses of etoposide and DACTINomycin. This problem is usually overcome with G-CSF and increased frequency (four doses daily) and duration (up to 4 days) of folinic acid rescue. Rescue should start 24 h after start of methotrexate infusion (3).

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					
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.			
vinCRIStine	No dose reduction necessary		**Bilirubin (micromol/L**		**AST/ALT (Units)**	**Dose**
			26-51	or	60-180	50%
			>51	and	Normal	50%
			>51	and	>180	Omit
Cyclophosphamide	**CrCl (ml/min)**	**Dose**	Not recommended in patients with a bilirubin >17micromol/L or serum transaminases or ALP more than 2-3 x upper limit of normal. In all such cases doses should be reduced			
	>20	100%				
	10-20	75%				
	<10	50%				
	Clinical decision-Consider whether patient is being treated with high dose treatment					

Management of adverse events:

Table 2: Dose Modification for Adverse Events

Adverse reactions	Recommended dose modification
Peripheral neuropathy Grade 2 Grade ≥3	Reduce vinCRIStine dose by 25%. If persists, reduce vinCRIStine by 50%. Omit vinCRIStine.
Mucositis and stomatitis or Diarrhoea Grade 3 1st occurrence:	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follows: Reduce DACTINomycin, etoposide, methotrexate, vinCRIStine and cyclophosphamide by 25%.

2nd occurrence:	Reduce DACTINomycin, etoposide, methotrexate, vinCRIStine and cyclophosphamide by 50%.
Grade 4: 1st occurrence:	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follows: Reduce DACTINomycin, etoposide, methotrexate, vinCRIStine and cyclophosphamide by 50%.
2nd occurrence:	Stop treatment.
Third space fluids (ascites, pleural effusions, very large ovarian cysts)	Hold methotrexate until recovery.
Malignant lymphoma	Discontinue.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

DACTINomycin Moderate (**Refer to local policy).**
Etoposide Low (**Refer to local policy).**
Methotrexate Moderate (**Refer to local policy).**
vinCRIStine Minimal (**Refer to local policy).**
Cyclophosphamide Moderate (**Refer to local policy).**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

G-CSF may be used to mitigate the risk of haematological toxicities.
Prophylactic laxatives to prevent constipation related to the use of vinca alkaloids.

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

Etoposide:

- **Hypersensitivity**: There is a high risk of hypersensitivity reactions with etoposide. Monitor infusion of etoposide for the first 15 minutes for signs of hypotension.

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.

vinCRIStine:

- **Neuropathy:** VinCRIStine may cause peripheral neuropathy which is dose related and cumulative, requiring monitoring before each dose is administered. The presence of pre-existing neuropathies or previous treatment with other neurotoxic drugs may increase risk of peripheral neuropathy. Patients with mild peripheral neuropathy can usually continue to receive full doses of vinCRIStine, but when symptoms increase in severity and interfere with neurologic function, dose reduction or discontinuation of the drug may be necessary. The natural history following discontinuation of treatment is gradual improvement, which may take up to several months. A routine prophylactic regimen against constipation is recommended for all patients receiving vinCRIStine sulphate. Paralytic ileus may occur. The ileus will reverse itself upon temporary discontinuance of vinCRIStine and with symptomatic care.

DRUG INTERACTIONS:

- CYP3A4 inducers may increase the clearance of etoposide and vinCRIStine.
- CYP3A4 inhibitors may decrease the clearance of etoposide and vinCRIStine.
- 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	01/02/2016		Prof Maccon Keane
2	07/02/2018	Updated with new NCCP regimen template and updated dosing in renal and hepatic impairment	Prof Maccon Keane
3	06/01/2021	Indication for use updated, treatment wording updated. Updated exclusion criteria. Updated hCG monitoring requirements. Standardisation of cyclophosphamide infusion volume and recommendations in hepatic impairment Updated emetogenic potential and adverse events section.	Prof Seamus O'Reilly
4	22/10/2021	Updated hCG testing in Tests (baseline and regular)	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.