**Etoposide Cisplatin/Etoposide Methotrexate Actinomycin D (EP/EMA) Therapy**

**INDICATIONS FOR USE:**

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Protocol Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of women with high-risk Gestational Trophoblastic Neoplasia (GTN) who have not responded or have relapsed from treatment with EMA/CO.</td>
<td>D39</td>
<td>00264a</td>
</tr>
<tr>
<td>GTN and hepatic metastases Women with GTN and hepatic metastases at presentation</td>
<td>D39</td>
<td>00264b</td>
</tr>
</tbody>
</table>

**ELIGIBILITY:**
- Indications as above

**EXCLUSIONS:**
- Hypersensitivity to etoposide, cisplatin, methotrexate, actinomycin D, or any of the excipients.

**TESTS:**
- **Baseline tests:**
  - FBC U&Es, LFTs, creatinine
  - human chorionic gonadotropin (hCG)
- **Regular tests:**
  - FBC, U&Es, LFTs, creatinine
  - 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.
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 patient’s individual clinical circumstances.

Treatment with etoposide and cisplatin (EP) alternates every 7 days with etoposide, methotrexate and actinomycin D (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 normalization 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.

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Etoposide</td>
<td>150mg/m²</td>
<td>IV</td>
<td>*1000 ml 0.9% NaCl over 60mins</td>
</tr>
<tr>
<td>1</td>
<td>Cisplatin</td>
<td>75mg/m²</td>
<td>IV</td>
<td>500-1000ml NaCl 0.9% over 2 hours (Pre and Post hydration therapy required)**</td>
</tr>
<tr>
<td>8</td>
<td>Actinomycin D</td>
<td>0.5mg</td>
<td>IV Bolus</td>
<td>n/a</td>
</tr>
<tr>
<td>8</td>
<td>Etoposide</td>
<td>100mg/m²</td>
<td>IV</td>
<td>1000 ml 0.9% NaCl over 30mins</td>
</tr>
<tr>
<td>8</td>
<td>Methotrexate</td>
<td>300mg/m²</td>
<td>IV</td>
<td>1000ml 0.9% NaCl over 12 hours</td>
</tr>
<tr>
<td>8</td>
<td>Folinic Acid</td>
<td>15mg</td>
<td>PO</td>
<td>Every 12 hours for 4 doses (to be started 24hrs after start of methotrexate)</td>
</tr>
</tbody>
</table>

*Refer to local policy re stability of etoposide infusion
Hypotension following rapid IV administration has been reported. Recommended that etoposide be administered over a 30-60min period.
Longer infusion times may be required based on the patient’s tolerance

**Pre and post hydration therapy required for cisplatin (Reference NCCP protocol 240 ECF Therapy for guidelines or see local hospital policy recommendations for Cisplatin Hydration)

DOSE MODIFICATIONS:
- Any dose modification should be discussed with a Consultant
- In general treatment may proceed if neutrophils ≥ 1 x10⁹/L and platelets > 75 x10⁹/L.
- The use of G-CSF support may be considered
Renal impairment:
Cisplatin
If serum creatinine increases by 25% or exceeds 1.5xULN or if patient generally unwell creatinine clearance should be repeated and consultant advice sought.

% of full dose to be given = \( \frac{\text{Actual GFR} \times 100}{\text{Predicted GFR}} \)

Methotrexate
If CrCl exceeds ULN, request consultant in charge to advise on methotrexate and folinic acid dose.

Hepatic dysfunction: Review methotrexate dosing with consultant.

Table 1: Dose modification schedule based on adverse events

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Discontinue</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis</td>
<td></td>
<td>Consider doubling folinic acid both in dose and duration before considering reduction in the dose of methotrexate.</td>
</tr>
<tr>
<td>Third space fluids (ascites, pleural effusions, very large ovarian cysts)</td>
<td></td>
<td>Hold methotrexate until recovery.</td>
</tr>
</tbody>
</table>

SUPPORTIVE CARE:
EMETOGENIC POTENTIAL: High (Refer to local policy).

PREMEDICATIONS:
Prehydration therapy for cisplatin according to local policy or as detailed in NCCP protocol 240 ECF Therapy.

TAKE HOME MEDICATIONS:
None usually required

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**: 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**: Actinomycin D can cause pain and tissue necrosis if extravasated.

**DRUG INTERACTIONS:**

- CYP3A4 inducers may increase the clearance of etoposide.
- CYP3A4 inhibitors may decrease the clearance of etoposide. Patients should also be counselled with regard to consumption of grapefruit juice.
- Cisplatin may potentiate the nephrotoxic and ototoxic effects of loop diuretics and aminoglycosides so concurrent use should be avoided.
- 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.

**ATC CODE:**

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<thead>
<tr>
<th>Drug</th>
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<tbody>
<tr>
<td>Etoposide</td>
<td>L01CB01</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>L01XA01</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>L01BA01</td>
</tr>
<tr>
<td>Actinomycin D</td>
<td>L01DA01</td>
</tr>
<tr>
<td>Folinic Acid</td>
<td>V03AF03</td>
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</table>

**REIMBURSEMENT CATEGORY:**

<table>
<thead>
<tr>
<th>NCCP Protocol: EP/EMA</th>
<th>Published: 20/06/2016</th>
<th>Version number: 1</th>
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<tbody>
<tr>
<td>Tumour Group: Gynaecology NCCP Protocol Code: 00264</td>
<td>Review: 20/06/2018</td>
<td>ISMO Contributor: Dr Maccon Keane</td>
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This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoprotocols.
Etoposide, cisplatin, methotrexate, actinomycin D and folinic acid are funded through local hospital budgets (April 2015).

**PRESCRIPTIVE AUTHORITY:**
Consultant medical oncologist experienced in the management of Gestational Trophoblastic Disease.

**REFERENCES:**
2. May T, Goldstein DP et al. Current Chemotherapeutic Management of Patients with Gestational Trophoblastic Neoplasia Chemotherapy Research and Practice 2011;Article ID 806256,

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>18/01/2016</td>
<td>Initial Draft</td>
<td>Dr Maccon Keane</td>
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Comments and feedback welcome at oncologydrugs@cancercontrol.ie.