# Peer Review Report #2

**Gestational Trophoblastic Neoplasia (GTN)**

Proposed medicines(s) for treatment of Gestational Trophoblastic Neoplasia (refer to application for specific protocols):

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Currently on EML</th>
<th>Addition</th>
</tr>
</thead>
<tbody>
<tr>
<td>methotrexate</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>leucovorin (= calcium folinate, folinic acid (INN))</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>actinomycin-D (dactinomycin)</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>etoposide</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>vincristine</td>
<td>✗</td>
<td></td>
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</table>

(1) Does the application adequately address the issue of the public health need for the treatment of the disease?

Yes ✔ No □

1. Relatively rare: As per the application, “choriocarinoma, a subset of GTN, affects 1 in 40,000 pregnancies in Europe and North America versus 9.2 in 40,000 pregnancies in Southeast Asia and Japan”
2. Affects relatively young age group women
3. As per the application: “Invasive mole and choriocarcinoma, which make up the vast majority of these tumors, always produce substantial amounts of human chorionic gonadotropin (hCG) and are highly responsive to chemotherapy with an overall cure rate exceeding 90%, making it usually possible to achieve cure while preserving fertility”
4. Fertility is restored with successful treatment
5. Chemotherapy is associated with cure rates >90% even in patients with widespread metastases.

(2) Have all important studies that you are aware of been included in the application?

Yes ✔ No □

1. Application gives two systematic reviews. Lack of strong evidence based on high quality RCTs was observed in these systematic reviews, probably due to the rarity of the condition
Does the application provide adequate evidence of efficacy/effectiveness of the proposed treatment regimen(s)?

Yes ☐  No ☑

1. Only two systematic reviews have been provided, the evidence is limited, may be due to rarity of the condition

<table>
<thead>
<tr>
<th>Description</th>
<th>Outcome</th>
<th>Magnitude of clinical benefit</th>
<th>Comment</th>
</tr>
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<tbody>
<tr>
<td>To determine which chemotherapy regimen/s for the treatment of resistant or relapsed GTN is/are the most effective and the least toxic (Cochrane Database Syst Rev, 2012;12: CD008891)</td>
<td>No RCTs identified in the review</td>
<td>Only Author’s conclusion</td>
<td></td>
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<tr>
<td>To determine the efficacy and safety of first line chemotherapy in the treatment of low-risk GTN five moderate to high quality RCTs (517 women): All compared methotrexate with dactinomycin</td>
<td>Rates of primary cure Dactinomycin better than methotrexate</td>
<td>Five studies, 513 women; RR 0.64, 95% Confidence Interval (CI) 0.54 to 0.76.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment failure Methotrexate &gt; Dactinomycin</td>
<td>(five studies, 513 women; RR 3.81, 95% CI 1.64 to 8.86).</td>
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<tr>
<td></td>
<td>Nausea – no difference</td>
<td>No difference (four studies, 466 women; RR 0.61, 95% CI 0.29 to 1.26)</td>
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<tr>
<td></td>
<td>Severe side effects – No difference</td>
<td>five studies, 515 women; RR 0.35, 95% CI 0.08 to 1.66; I² = 60%),</td>
<td></td>
</tr>
</tbody>
</table>

2. Remission rates are given for single therapy – However, no references are given

Does the application provide adequate evidence of safety for the proposed treatment regimen(s)? Are there any adverse effects of concern, or that may require special monitoring?

Yes ☑ ☑ ☐  No ☐
1. Application list the side effects of the agents indicated in the treatment. However, there is no study data.
2. Any cytotoxic therapy has its own side effects which cannot be avoided altogether
3. Precautions are important
4. Considering the public health relevance of the condition and successfulness of treatment a trade off with its’ potential side effects is acceptable
5. See above Table as well

ADDITIONAL CONSIDERATIONS:

(5) Are there special requirements or training needed for the safe, effective and/or appropriate use of the proposed treatment(s)?

Yes ☑ No ☐

1. Administration requires intravenous infusion capacity, and requires the patient to have regular access to clinical care
2. IV hydration and anti-emetics should accompany administration of most agents.
3. Monitoring requires that clinicians have access to laboratory facilities, as well as the ability to recognize and address potential toxicities caused by the treatment itself, including but not limited to bone marrow suppression, infection, allergic reactions, and gastrointestinal toxicity.
4. However, these are basic facilities in a centre which treats cancer

(6) Are there any issues regarding the registration of the proposed medicines by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes ☐ No ☑

(7) Comment briefly on issues regarding cost and affordability of treatment.

1. Application has not presented the data
2. Because of its rarity, treatability, epidemiology (affected age, etc) and preserving fertility, cost and affordability should play a secondary role in the decision making

(8) Any additional comments on the application?

No

(9) Please summarise the action(s) you propose the Expert Committee take.

To include methotrexate and Dactinomycin as both have some evidence