Proposed medicines(s) for treatment of Ewing Sarcoma (refer to application for specific protocols):

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Currently on EMLc for other indications</th>
<th>Addition to EMLc for Ewing Sarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>vincristine</td>
<td>☒</td>
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</tr>
<tr>
<td>doxorubicin</td>
<td>☒</td>
<td>☒</td>
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<tr>
<td>cyclophosphamide</td>
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<td>☒</td>
</tr>
<tr>
<td>ifosfamide</td>
<td>☐</td>
<td>☒</td>
</tr>
<tr>
<td>etoposide</td>
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</tbody>
</table>

(1) Does the application adequately address the issue of the public health need for the treatment of the disease? Yes ☒ No ☐

Comments:
Primary bone tumors account for 5% of all cancers in childhood and Ewing sarcoma is the second most common bone tumor in this age group. For patients with localized disease 5-year survival rates of approximately 70% are achieved with current protocols.

(2) Have all important studies that you are aware of been included in the application? Yes ☐ No ☒

Comments:
The approach is not based on studies but on protocols (in use in developed countries) for the type of disease in the paediatric age group. These protocols include combination chemotherapy and ancillary medicines. Paediatric protocols are based on clinical trials, but the trials as such are not presented in the application in detail.

(3) Does the application provide adequate evidence of efficacy/effectiveness of the proposed treatment regimen(s)? Yes ☒ No ☐

Comments:
For patients with localized disease the strategy of neo-adjuvant multi-agent chemotherapy followed by local control (surgery/radiotherapy) then further chemotherapy has achieved 5-year survival rates of approximately 70%.
(4) **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 ☐

Comments:
Many types of toxicity are associated with the protocols. Vincristine commonly causes neurotoxicity. Doxorubicin is associated with a risk of cardiotoxicity. Cyclophosphamide has high risk of bladder toxicity. Ifosfamide can cause bladder toxicity. The most frequent dose-limiting toxicity for etoposide is myelosuppression, primarily leukopenia which can be grade 3-4 in >10% of patients. Etoposide can also cause hypersensitivity reactions, reversible alopecia in up to 60% of patients. The use of etoposide has been associated with an increased risk of a second cancer.

**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 ☐

Comments:
Diagnostics, surgery/radiotherapy require appropriate equipment and training, as does also multi-agent chemotherapy.

(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 ☒

Comments:

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

All medicines proposed to EMLc are already on the EML. New would be ifosfamide powder for injection 500 mg vials, which is less expensive than the 2 g vial already on the EML.

(8) **Any additional comments on the application?**

Application does not make any suggestions on the formulations and strengths to be included.

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

Add vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide to EMLc Complementary list under Ewing Sarcoma in the formulations already available on EML and EMLc., and for ifosfamide 500 mg vial. Add Ewing sarcoma also be as a cancer to the EML Complementary list as peak of incidence is in the 2nd decade of life, which is partly outside the EMLc age limit of 12 yrs.