Proposed medicines(s) for treatment of Retinoblastoma (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 Rhabdomyosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>vincristine</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>ifosfamide</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>actinomycin-D (dactinomycin)</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

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

Yes ☒ No ☐

Comments:
Rhabdomyosarcoma (RMS) found most commonly in children and adolescents younger than 20 years old, accounting for approximately 40% of all pediatric soft tissue sarcomas worldwide. RMS incidence in the US is estimate to be 4.5 cases per million children/adolescents per year with more than 50% of cases occurring in children younger than age 10 years.

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

Yes ☐ No ☒

Comments:
The approach of the application 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:
The overall outcome of RMS patients with localized disease is currently around 70%, but is strictly correlated to the risk group.
(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:
Patients treated with ifosfamide have a high risk of bladder toxicity, cyclophosphamide can also cause bladder toxicity. Vincristine commonly causes neurotoxicity, actinomycin-D is associated with high emetic potential.

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:
Pre-treatment assessment for risk-adaptation requires appropriate equipment and training. Treatment requires intravenous infusion capacity, radiotherapy and also requires that the patient have regular access to expert clinical care.

(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.
With the protocols proposed, costs in the same range as other cancer treatments already included on EML/EMLc.

(8) Any additional comments on the application?
Vincristine, actinomycin-D (dactinomycin) and cyclophosphamide are currently on EML and EMLc, ifosfamide is on EML for adults.
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, actinomycin-D (dactinomycin), and ifosfamide to EMLc Complementary list under Rhabdomyosarcoma, in the formulations already available on EML and EMLc, and for ifosfamide additionally 500 mg vial to EMLc.
Add vincristine, actinomycin-D (dactinomycin), and ifosfamide to EML Complementary list under Rhabdomyosarcoma.