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 Retinoblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>vincristine</td>
<td>☒</td>
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<tr>
<td>carboplatin</td>
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<td>☒</td>
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<tr>
<td>cisplatin</td>
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<td>☒</td>
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<tr>
<td>etoposide</td>
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(1) Does the application adequately address the issue of the public health need for the treatment of the disease?

Yes ☐ No ☐

Comments:
Retinoblastoma is the most frequent neoplasm of the eye in childhood, and represents 3% of all childhood malignancies. It is a cancer of the very young; two-thirds are diagnosed before 2 years of age, and 95% before 5 years. For these reasons, therapeutic approaches need to consider not only the cure of the disease but also the need to preserve vision with minimal long-term side effects.
Incidence appears to be higher (6-10/106 children) in Africa, India, and among children of Native American descent in the North American continent.
The estimated incidence of retinoblastoma is 1 in 16,000-18,000 births annually with between 7000 and 8000 new cases per year worldwide. The annual incidence is 3.5 per million children younger than 15 and 11.8 per million children younger than 5 years of age.

(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 ☐
Intraocular disease is highly curable; more than 90% of patients survive. If the disease is limited to the orbit, a combination of chemotherapy, surgery, and radiation therapy may be effective and cure 50-70% of patients.

(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?

Comments:
Vincristine commonly causes neurotoxicity, the most frequent dose-limiting toxicity for etoposide is myelosuppression, platinum agents including cisplatin and carboplatin cause myelosuppression with dose-limiting thrombocytopenia, renal toxicity caused by cisplatin can be significant, cyclophosphamide can cause bladder toxicity. Pediatric patients treated for retinoblastoma have a significant risk of developing secondary malignancies, risk may be as high as 35%.

ADDITIONAL CONSIDERATIONS:

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

Comments:
Required for diagnosis, particularly to evaluate extra-ocular extension. While some forms of chemotherapy are not very demanding (for a chemotherapy), other forms like chemotherapy in ophthalmic artery require special training and equipment. Also the age of the patients adds to the challenges.

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

Comments:

(7) Comment briefly on issues regarding cost and affordability of treatment.
All except cisplatin are already on EML/EMLc, cisplatin is less expensive than carboplatin.

(8) Any additional comments on the application?
Vincristine is currently on EML and EMLc, etoposide and carboplatin are on EML for adults, cisplatin is currently not on the EML or EMLc. 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, carboplatin, and etoposide to EMLc Complementary list under Retinoblastoma, in the formulations already available on EML and EMLc (perhaps with the exclusion of some of the largest vials?). Add cisplatin to EMLc Complementary list under Retinoblastoma, in the formulations: 1 mg/ml concentrate for infusion in 10 ml, 50 ml and 100 ml (?) vials.