Proposed medicines(s) for treatment of Rhabdomyosarcoma (paediatric) (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>
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<tr>
<td>cyclophosphamide</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 ☐

Rhabdomyosarcoma is the most frequently occurring soft tissue sarcoma in children. A long series of studies conducted by the Intergroup Rhabdomyosarcoma Study Group (IRSG), its successor, the Soft Tissue Sarcoma Committee of the Children’s Oncology Group, and studies of soft tissue sarcomas conducted by European investigators have confirmed the efficacy of the application of the three or four most active chemotherapeutic agents for management: Vincristine, dactinomycin, cyclophosphamide, and ifosfamide. The administration of ifosfamide requires availability of MESNA as well as anti-emetics and other supportive care.

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

Yes ☒ No ☐

The history of the development of successful management of rhabdomyosarcoma involves many studies reported in hundreds of relevant manuscripts. Key review manuscripts are included in the application, but numerous others could be cited to document the efficacy of the drugs proposed in this application.

(3) Does the application provide adequate evidence of efficacy/effectiveness of the proposed treatment regimen(s)?

Yes ☒ No ☐
Children with rhabdomyosarcoma had a poor outcome prior to the chemotherapy era. Even those patients presenting with localized tumors which could be controlled surgically or with irradiation ultimately died of metastatic disease. The use of multi-drug chemotherapy adjuvantly in conjunction with local control measures for the primary tumor have resulted in cure rates of close to 70% using modern regimens in the setting of multi-disciplinary care in high income countries. Thus, the impact of chemotherapy on the outcome for these children is indisputable. The prognosis for children presenting with overt metastatic disease remains less favorable. The utility of all drugs proposed in the application has been confirmed in randomized controlled trials.

(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 ☐

The regimens used for this tumor incorporate drugs that have been in use for decades. The acute and late toxicities of therapy are well known and are well described in the “Harms and Toxicity Considerations” section of the application. Toxicities of therapy and potential complications have been well described and are manageable in centers with appropriate experience.

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 ☐

The relative rarity of the tumor mandates that therapy should be undertaken in centers with appropriate diagnostic and therapeutic expertise and the availability of suitable supportive care facilities and specialists able to provide local control therapies. Toxicities of therapy and potential complications have been well described and are manageable in centers with appropriate experience.

(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 ☒

Drugs utilized in the regimen are relatively old, off-patent with well-described acute and late toxicities. As is true for many of the older chemotherapeutic agents used in
children, it is unclear that any of these drugs are labelled specifically for use in rhabdomyosarcoma.

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

The proposed drugs are off patent and relatively inexpensive.

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

Regimens that have proven to be successful for management of rhabdomyosarcoma incorporate the same drugs and are used universally. The best results are achieved with the three or four drugs mentioned; differences among accepted regimens result from relatively subtle differences in drugs, dosing and scheduling.

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

Addition of vincristine, dactinomycin, cyclophosphamide, ifosfamide, and MESNA to the List of Essential cytotoxic and adjuvant medicines for use in children with rhabdomyosarcoma. Vincristine, dactinomycin, and cyclophosphamide are already on the WHO Model List of Essential medicines for other pediatric cancers. Ifosfamide is being recommended for inclusion on the List of Essential Medicines for Pediatrics; it is already on the List of Essential cytotoxic and adjuvant medicines for use in adults. Administration of ifosfamide requires co-administration of MESNA (which is already on the list of essential anti-neoplastic medicines for use in adults).