Proposed medicines(s) for treatment of Hodgkin Lymphoma (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 Hodgkin Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>vincristine</td>
<td>☒</td>
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<tr>
<td>doxorubicin</td>
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<tr>
<td>cyclophosphamide</td>
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<tr>
<td>prednisone</td>
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<tr>
<td>etoposide</td>
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<td>☒</td>
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<tr>
<td>bleomycin</td>
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<tr>
<td>dacarbazine</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:
The application addressed that pediatric Hodgkin lymphoma (pHL) is the most common malignancy among adolescents 15-19 years of age and is epidemiologically distinct from adult HL. This challenge has resulted in the development of various strategies aimed at identifying the optimal balance between maintaining overall survival and avoidance of long-term morbidity of therapy. The core treatments are variably combined chemotherapies including etoposide and dacarbazine. We agreed the application description.

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

Yes ☐ No ☒

Comments:
The application contained most of the important studies, but missed some clinical studies and some Chinese studies. We added one Chinese guideline and 10 clinical studies containing 599 patients, using etoposide and dacarbazine. Chemotherapy regimen is different between our searches and the application, such as vinblastine, bleomycin, etoposide (VP16), and prednisone (VBVP). But the effectiveness and safety are nearly same.
(3) Does the application provide adequate evidence of efficacy/effectiveness of the proposed treatment regimen(s)?

Yes ☑ No ☐

Comments:

The application recommended chemotherapy regimens included etoposide and dacarbazine for the treatment of pHL such as OEPA (vincristine, etoposide, prednisone, and doxorubicin) for standard risk patients, ABVE-PC: (doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide), OEPA/COPDac (vincristine, etoposide, prednisone, and doxorubicin)- cyclophosphamide, vincristine, prednisone, and dacarbazine) for intermediate or high risk patients. The overall survival is good and the toxicities are well tolerated. We agreed the application description.

(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:

The application considered the safety and adverse effects of the proposed regimens. Pediatric patients being treated with vincristine, doxorubicin, cyclophosphamide, prednisone, etoposide, bleomycin and dacarbazine must be carefully monitored. Vincristine commonly causes neurotoxicity. Treatment with bleomycin may result in late bleomycin-related pulmonary toxicity. Doxorubicin is associated with a risk of cardiotoxicity. Etoposide and dacarbazine are at risk of secondary malignancy. Cyclophosphamide are also at risk for infertility. So closely monitoring should be done in the infusion site for possible infiltration during drug administration. We agreed the application description.

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:

The application described that anticancer medicines should be undertaken only in a specialized cancer center by well-trained medical personnel. We support the application comments and also suggested long sleeved gowns, protection masks, caps, gloves are recommended for protection of users.

(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:

The application missed this issue.
We searched regulatory authorities such as FDA (Food and Drug Administration), EMA (European Medicines Agency) and CFDA (China Food and Drug Administration). The results showed that both etoposide and dacarbazine had not been registered for pediatric Hodgkin Lymphoma indication and had no pediatric dosage yet.

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

The application missed this issue.
The evidence from our added studies demonstrated that the total cost of treatment for pediatric HL is affordable for developed countries, but not for developing countries. In Daniela study, the cost of ABVD 4-6 cycles in Africa is $340-510. If calculate the diagnosing, treating with chemotherapy and following up a child with stage 2 HL for 2 years post-therapy, the total cost was $6647.27, which more than 3 times of GDP per person in Africa.

(8) **Any additional comments on the application?**
None.

(9) **Please summarise the action(s) you propose the Expert Committee take.**
We recommend etoposide and dacarbazine been incorporated for Section 8.2 of the WHO EMLc. But they should approved by regulatory authorities for pediatric management.