Proposed medicines(s) for treatment of Osteosarcoma (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 Osteosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>doxorubicin</td>
<td>☒</td>
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</tr>
<tr>
<td>cisplatin</td>
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<tr>
<td>methotrexate</td>
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<tr>
<td>carboplatin</td>
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<tr>
<td>ifosfamide</td>
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</table>

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

Yes ☒ No ☐

Comments:
Osteosarcoma is the most common primary malignant bone tumor in children and young adults and accounts for 5% of all pediatric malignancies, and the eighth most common cancer in children and adolescents. The overall survival for children with localized disease is approximately 70%.

Data collected in several countries from 1968-1997 to determine the global incidence and distribution of osteosarcoma in children. These data estimated the global incidence rate to be between 3 to 4.5 cases per 1 million children, adolescents, and young adults (0-24 years of age) per year (2). The incidence rates were estimated to be relatively consistent throughout the world.

(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:
The 6-year overall survival for localized osteosarcoma patients is 70-78% with current protocols.

(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:
Cisplatin can cause severe nausea and vomiting and requires administration of prophylactic anti-emetics. It is preferable to administer chemotherapy using a centrally placed intravenous catheter. Doxorubicin extravasation can lead to local tissue injury and necrosis. Methotrexate-containing regimens require frequent monitoring of methotrexate levels, intravenous hydration, urinary alkalinization and folinic acid rescue. High cumulative dose of doxorubicin leads to risk of cardiac toxicity. Supportive care with G-CSF administration may be required to ensure timely therapy, especially towards the end of treatment.

ADDITIONAL CONSIDERATIONS:

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

Comments:
Diagnostics, surgery 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)

Comments:

(7)  Comment briefly on issues regarding cost and affordability of treatment.
All medicines proposed to EMLc except cisplatin are already on the EML. Cisplatin is in line with cost of the other medicines in the protocols.

(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 cisplatin 1 mg/ml 50ml and 100 ml vial, carboplatin as in EML, and ifosfamide as in EML and additionally 500 mg vial to EMLc Complementary list under Osteosarcoma. Osteosarcoma should also be added 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.