Osteosarcoma (paediatric)

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>
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</thead>
<tbody>
<tr>
<td>doxorubicin</td>
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<tr>
<td>cisplatin</td>
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<tr>
<td>methotrexate</td>
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<td>carboplatin</td>
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<td>ifosfamide</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 ☐

Osteosarcoma is the most frequently occurring bone tumor in children and adolescents. Randomized studies have confirmed the benefit of the application of adjuvant chemotherapy for management, although a variety of regimens have proven to be effective. Most regimens incorporate cisplatin, doxorubicin, and high dose methotrexate with leucovorin rescue (HDMTX) although the contribution of HDMTX has remained controversial. Ifosfamide has also proven to be an active agent. The administration of these agents requires anti-emetics and other supportive care. The administration of HDMTX is potentially lethal and requires careful monitoring of methotrexate excretion.

(2) Have all important studies that you are aware of been included in the application?  
   Yes ☐ No ☒

Although HDMTX is a component of most regimens in use in developed countries, its contribution to the efficacy of adjuvant regimens remains controversial. In a randomized study, the outcome of patients treated with doxorubicin/cisplatin plus HDMTX was comparable to the outcome for patients treated only with doxorubicin/cisplatin. The results were published in: Bramwell VH, Burgers M, Sneath R, Souhami R, van Oosterom AT, Voute PA, Rouesse J, Spooner D, Craft AW, Somers R, et al.: A comparison of two short intensive adjuvant chemotherapy regimens in operable osteosarcoma of limbs in children and young adults: the first
study of the European Osteosarcoma Intergroup. J Clin Oncol 10:1579-91, 1992. Although this is the only study that specifically addressed the role of HDMTX in osteosarcoma, regimens that include HDMTX have resulted in better outcomes than regimens that do not include it.

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

Yes ☐ No ☑

The efficacy of adjuvant chemotherapy in management of osteosarcoma is indisputable. The most effective regimens feature doxorubicin, cisplatin and HDMTX. The OS99 study testing carboplatin, ifosfamide and doxorubicin was studied in only 72 patients, and this regimen has not been adopted widely.

(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.

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 other than HDMTX are labelled specifically for use in osteosarcoma. Noteworthy is that dexrazoxane which is recommended as a cardioprotectant because of the high cumulative doses of doxorubicin prescribed in the successful regimens is not universally available.

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

The proposed drugs are off patent and relatively inexpensive, although administration of HDMTX requires monitoring of drug levels and aggressive supportive care if methotrexate excretion is delayed.

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

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

Addition of doxorubicin, cisplatin, methotrexate (specifically HDMTX with leucovorin rescue), carboplatin, ifosfamide, and MESNA to the List of Essential cytotoxic and adjuvant medicines for use in osteosarcoma. Doxorubicin and methotrexate 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). Administration of High Dose Methotrexate mandates the use of leucovorin “rescue.” It does not appear to be on the List of Essential cytotoxic and adjuvant medicines for use in adults or children, but it would have to be included if HDMTX is included. Cisplatin is not on the List of Essential cytotoxic and adjuvant medicines for use in adults or children, but it should be.