I.11	Doxorubicin - rhabdomyosarcoma
Does the application adequately address the issue of the public health need for the medicine?	☐ Yes ☒ No ☐ Not applicable Comments: Actually in this submission that is far from exhaustive this issue is not addressed
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	Sadly, the role of doxorubicin in rhabdomyosarcoma remains controversial. Less controversial is its use as a single agent – an approach that has no support. The controversy is the extent to which the addition of doxorubicin to combinations of chemotherapy agents can improve efficacy and the extent to which it might worsen toxicity.
Have all important studies and all relevant evidence been included in the application?	☐ Yes ☒ No ☐ Not applicable Comments: The application is far from exhaustive and includes only two clinical references of any value. One reports on the results of two consecutive trials of dose-intensive chemotherapy with doxorubicin and ifosfamide in patients with sarcomas. It is advanced as a "surrogate" for doxorubicin efficacy. While some of the results were impressive the report does not properly address the value of doxorubicin but instead the value of adding doxorubicin to ifosfamide. Additionally it enrolled patients with all sarcomas not just rhabdomyosarcomas. The second "relevant reference" describes the results of adding dose-intensified doxorubicin to standard chemotherapy for rhabdomyosarcoma, in this context the IVA regimen [ifosfamide + vincristine + dactinomycin] used in the EpSSG RMS 2005 trial. The latter trial many had hoped would put to rest the issue of the value of doxorubicin by demonstrating superior efficacy but unfortunately did not turn out as those who thought it would advocate for doxorubicin use had hoped.
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☐ Yes ☒ No ☐ Not applicable Comments: The reports on the results of two consecutive trials of dose-intensive chemotherapy with doxorubicin and ifosfamide in patients with sarcomas is not randomized and difficult to compare. In the publication reporting the results of the EpSSG RMS 2005 trial the authors concluded "The addition of dose-intensified doxorubicin to standard IVA chemotherapy did not show a significant improvement in the outcome of patients with high-risk non-metastatic rhabdomyosarcoma. Therefore, the IVA chemotherapy regimen should remain the standard of care for patients with localised rhabdomyosarcoma in Europe."
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☐ Yes ☒ No ☐ Not applicable Comments: Safety in the sense that it could safely be given in the context of a clinical trial is supported by the two references cited. But in considering this submission and in thinking about safety one must go beyond the clinical trial setting to the real-world settings where this would be employed. In that equation safety is less clear. In EpSSG RMS 205, several toxicities were significantly more common in the IVA plus doxorubicin cohort than in the IVA group including: grade 3-4 leucopenia in 232/249 [93%] patients in the IVA plus doxorubicin group vs 194/227 [85%] in the IVA group; p=0·0061), anemia in 195/249 [78%] vs 111/227 [49%]; p<0·0001), thrombocytopenia in 168/249 [67%] vs 59/227 [26%]; p<0.0001), and gastrointestinal adverse events in 78/249 [31%] vs 19/227 [8%]; p<0·0001). Additionally, grade 3-5 infections 198/249 [79%] vs 128/227 [56%]; p<0·0001) were also significantly more common in the IVA plus doxorubicin group than in the IVA group. While these data describe toxicity in aa combination regimen, they cannot be ignored given the only conclusion one can reach

	is that the addition of doxorubicin to the IVA regimen results in meaningfully greater toxicity. Also of concern is the statement that "cumulative doses above 550 mg/m^2 are associated with an increased risk of cardiomyopathy". A dose of 550 mg/m^2 is higher than the 400-450 mg/m^2 at which most would be concerned.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments: Special attention should be given to cardiotoxicity, especially in the very young, but this should not be considered "out of the ordinary" if the drugs are administered by properly trained professionals. However, the need to evaluate cardiac function at baseline and at intervals while treatment is administered adds a level of complexity to the administration of doxorubicin.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Unfortunately, one must conclude the benefit to risk ratio is not favourable. There is no evidence in the literature that can be cited in support of efficacy, including the references cited with the submission. Indeed, there is evidence in the cited references of greater toxicity, albeit when doxorubicin is added to other agents, without benefit. In the EpSSG 2005 study the 3-year event-free survival was 67.5% (95% CI 61.2-73.1) in the IVA plus doxorubicin group and 63.3% (56.8-69.0) in the IVA group (hazard ratio 0.87, 95%CI 0.65-1.16; p=0.33). However, 3-year overall survival trended in the direction of harm with rates of 78.3% (95%CI 72.4–83.0) in the IVA plus doxorubicin group versus 80.6% (74.9–85.1) in the IVA group (HR 1.17, 95%CI 0.82–1.67; p=0.37).
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	In its totality the overall quality of the evidence is poor as it is uninterpretable. It does not allow one to reach a conclusion as to in whom, at what dose, and in what schedule or drug combination is doxorubicin effective, if indeed effective. Differences in patient populations and the regimens and schedules utilized preclude cross-trial comparisons.
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: Cardiac function needs to be monitored and this can be done in several ways with echocardiography likely most widely available and cost-effective.
Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments:
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☒ Yes ☐ No ☐ Not applicable Comments:
Briefly summarize your assessment of any issues regarding access, cost, and affordability of the medicine in different settings.	As a chemotherapeutic agent for which many generic formulations are available the cost of doxorubicin should not be a concern. Monitoring of cardiac function would add some cost, but this should not be prohibitive.

Any additional comments	• The value of doxorubicin in the therapy of rhabdomyosarcoma remains unproven with disparate results in clinical trials. Comparisons are difficult given different enrolment criteria with differences in risk group assignment between Europe and North America confounding some studies. • There appears to be consensus that the use of doxorubicin in patients with low-risk rhabdomyosarcoma is not justified. The uncertainty is its use in those with high-risk rhabdomyosarcoma. • There was hope the EpSSG 2005 study would clarify the role of doxorubicin in high-risk rhabdomyosarcoma, but it did not – indeed it demonstrated greater toxicity without benefit in overall survival. • One can say with confidence that no trial has proven that doxorubicin is of value in any risk rhabdomyosarcoma.
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	Unfortunately, this was an unsatisfactory submission that left the question of what was being sought unanswered. Even the tile of the application – "Review of doxorubicin as a medicine for treatment of rhabdomyosarcoma on the WHO Model List of Essential Medicines" – is unclear. The data discussed in this review convincingly demonstrates that doxorubicin should not be used in individuals with low-risk rhabdomyosarcoma and that in combination regimens its efficacy is unproven and in the most robust randomized trial was more toxic and clearly not beneficial, even trending to harm. What the submission requests is uncertain. In the Summary Statement this is confusing: "Doxorubicin has been considered an effective therapeutic option as single agent before triplets become the standard. However, now the role of doxorubicin as an appropriate first-line chemotherapy option for advanced or metastatic rhabdomyosarcoma is controversial. **For this reason, we do not propose inclusion of doxorubicin on the Model List for this indication**". What is its request then? Later under Summary of Potential Benefits they note: "Doxorubicin has been considered an effective therapeutic option as single agent before triplets become the standard. With the addition of more medicines, e.g. ifosfamide, in combinations, **the role of doxorubicin and its contribution in terms of overall survival has become less certain. [5,6] This has led to discontinuation of doxorubicin by some authoritative therapeutic protocol. [7]**" Is the request then for the use of doxorubicin as a single agent as a first line option in settings where standard chemotherapy regimens such as IVAC and VAC are not available? This too is problematic and furthermore is not requested outright but can only be inferred. This would be problematic since it would be a WHO EML recommendation that lacks supporting evidence. In conclusion, given the lack of clarity, the lack of evidence and the fact doxorubicin is already included in the WHO EML List I would not be in favor of specifically providing support for its use in rhabdomyosarcoma
References (if required)	