F.1	Abacavir + lamivudine + lopinavir/ritonavir - HIV
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: There is no doubt that a paediatric dosage form of an important anti HIV medicines FDC is of very public health need
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.	As per the WHO guidelines, combination of these medicines ABC or AZT + 3TC + LPV/r is recommended as preferred therapy for children under the age of 3 years (ABC is preferred over AZT) In WHO EMLc, we already have 1. ABC dispersible or scored tablet 2. 3TC as oral liquid 3. LPV/r as oral liquid and solid dosage forms 4. Ritonavir – oral liquid, tablet and powder 5. FDC: ABC+ 3TC as dispersible, scored LPV/r: Pellets are also available in the market (some restrictions are there for the use of oral liquid in premature babies and full term babies up to 14 days of age) For children under 3 years, it had to be combination of product 5 and product 3 (dispersible and oral liquid) or even 1+2+3
Have all important studies and all relevant evidence been included in the application?	☐ Yes ☒ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included: This is for a new dosage form of a new FDC (4 in 1) Only one study – Reference links to the clinical trial registry entry Partial findings of this trial are given in the application
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☐ Yes ☒ No ☐ Not applicable Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). 29 children with 15 in the test arm and 14 in reference arm (later as cross-over, so 29-31 children were exposed to test FDC The proportion of children with VL<400 cp/mL increased from 88% **(29/33**) at baseline to 97% **(30/31**) at the end of the study. The proportion with VL<50 cp/mL increased from 48% **(16/33**) to 65% **(20/31**), when excluding the missing data. This paragraph was extracted from the application. Table is not very clear However, for a new dosage form of a new FDC, PK studies are very important. | | AUC | Cmax |

<table>
<tr><td></td><td>
<table>
<tr><td>ABC</td><td>GMR 94%. Bioequivalence criteria (BC): Met</td><td>GMR is 24% lower. Bioequivalence (BC) criteria: Not met</td></tr>
<tr><td>3ATC</td><td>GMR 82%.
BC: Not Met</td><td>GMR 69%
BC: Not met</td></tr>
<tr><td>LPv</td><td>GMR is 12% lower
BC: Not Met</td><td>GMR is 17% lower
BC: Not Met</td></tr>
<tr><td>R</td><td>GMR is 12% lower
BC: Not met</td><td>GMR is 18% lower
BC: Not met</td></tr>
</table>

Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? Not applicable. It is a paediatric dosage form</td></tr>
<tr><td>Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?</td><td>☐ Yes
☒ No
☐ Not applicable
Comments:
1. All the components in the proposed medicine are already in the EMLc
2. PK data showed that the AUC and Cmax of all 4 medicines was lower with 4 in 1 (test product) than the reference dosage form – Dose dependent AEs will be less with test product
3. Limited number of participants – Only very common AEs can be picked up
4. Proportion of TEAE is higher with test product (74% vs 56%)</td></tr>
<tr><td>Are there any adverse effects of concern, or that may require special monitoring?</td><td>☒ Yes
☐ No
☐ Not applicable
Comments: See above. Will be common to 4 individual medicines – They are already listed in EML</td></tr>
<tr><td>Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)</td><td>Uncertain</td></tr>
<tr><td>Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)</td><td>Low</td></tr>
<tr><td>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)</td><td>☒ Yes
☐ No
☐ Not applicable
Comments: Common to individual medicines in the FDC. Parents also have to be trained to administer the dosage form</td></tr>
</table>

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: Not registered with any authorities Not prequalified by the WHO?
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: See section 2 of this form Dosage form and this particular FDC is not recommended yet (though encouraged to develop)
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	Product is not in the market
Any additional comments	1. Details given in the application do not meet the requirements for a FDC (WHO) 2. No comparative data for infants < 3 Kg (Children in WB1 only received the 4-in-1 for 21 days) 3. Results of PK investigation for this new dosage form of this new FDC is not supportive to include this medicine into EMLc at this time 4. I did not see stability data
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.	NOT RECOMMENDED Though I understand the need for this product (FDI, oral granules), the available data is inadequate
References (if required)	