Expert peer review on application for inclusion/specification of formulations of antiretroviral medications in the EML (children)

- Abacavir – Tablet (dispersible): 60mg
- Efavirenz - Tablet (scored): 200 mg, split-table into 100 mg-doses
- Lamivudine + Nevirapine + Zidovudine - Tablet (dispersible): 30 mg + 50 mg + 60 mg
- Nevirapine - Tablet (dispersible): 50 mg (as hemihydrate) - Children
- Zidovudine + Lamivudine - Tablet (dispersible): 60 mg + 30 mg
- Stavudine + Lamivudine – Tablet (dispersible): 6 mg + 30 mg

Reason for these applications:
Children living with HIV-1 infection in resource-limited settings presently have limited treatment options for their infection. These formulations would improve access to treatment for children living with HIV.

Summary of applications:
The applications are for the inclusion/specification of formulations of medicines already included in the EML(c). Therefore, the sections on safety and efficacy are not included in this peer review, as they have already been assessed by previous expert committees. Only the information which is relevant and specific to the new suggested formulations is included.

Advantages to dispersible tablet formulations:
- More convenient for active pharmaceutical ingredients with insufficient stability in water;
- More easily transportable and they generate less handling and transportation costs for the same amount of active ingredient (less volume, less weight);
- Easier to produce and the production costs are less, which makes them more affordable than standard liquid formulations;
- Can be used in very young children (0 – 6 months) and can be dispersed in breast milk;
- Are easy to dispense and they require minimal manipulation by health professionals and parents prior to use which minimizes the risk of errors; and
- Dispersible with only a small amount of water for administration.

Advantages to scored tablet formulations:
As a scored tablet, this formulation is able to singly cover children who otherwise would be using the 100mg and 200mg tablets or capsules. In addition, scored tablets allow for ease of adapting dosage and utilizing one tablet across multiple weight bands.

The consolidation of volumes around a single product ensures:
- A more stable supply of efavirenz in the low-volume paediatric market;
- Reduced costs of production, storage, transport, dispensing and other health system costs; and
- Simplified supply systems

3. Assessment of cost and availability
a. Have all relevant data on cost and availability been provided
   Yes No (if no, please provide reference and information)

According to the WHO Towards Universal Access Progress Report in 2010 more than 57,000 children (15%) on HIV-1 therapy were treated with Abacavir-containing regimens across 45 low- and middle-income countries (excluding the Region of the Americas). No information was provided on availability.
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b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

**Abacavir:** Pricing data (2011) indicates the premium for dispersibility for the Abacavir 60mg tablet is approximately 24% over the standard tablet. Combining the pricing available for the non-dispersible formulation of ABC 60mg tablet with the dispersability premium indicates an average price per patient per year (PPPY) of USD $178. The dispersible formulation of Abacavir offers a significant price advantage over the syrup, costing approximately 36% less in PPPY terms.

**Efavirenz:** The application reports an average PPPY for the EFV (200mg) scored tablet of USD $41, while the 100mg capsule/tablet has a PPPY of $90 and the 50mg capsule/tablet is $130. Given that the 200mg scored tablet can be broken into 100mg doses, the formulation offers a price advantage over the 100mg and 50mg pills, costing approximately 54% and 68% less in PPPY terms, respectively.

**Lamivudine + Nevirapine + Zidovudine:** The price according to average pricing data from the WHO Global Price Reporting Mechanism (GPRM) is USD $0.070 per pill, or approximately USD $102.2 per patient per year. This FDC is currently only available in dispersible form, thus specifying dispersibility for this product will have no impact on pricing.

**Nevirapine:** The application reports an average price per patient per year (PPPY) for the NVP (50mg) dispersible tablet of USD $61 and state that this formulation offers a significant price advantage over the NVP 10mg/ml syrup, costing approximately 50% less in PPPY terms.

**Zidovudine + Lamivudine:** dispersible formulation received SRA approval in mid-2011, so there is limited pricing information. The application presents unpublished 2011 data indicating that the premium for dispersibility for the AZT/3TC 60mg + 30mg tablets to be approximately 22%. However, they argue that while there is such a price increase in this formulation, the dispersibility allows for the replacement of single syrups, resulting in price reductions. The dispersible formulation of AZT/3TC costs approximately 68% less than syrups in PPPY terms.

**Stavudine + Lamivudine:** The application reports an average PPPY for d4T/3TC (6mg/30mg) tablet of USD $50. The application states that this formulation offers a significant price advantage over the combined cost of the individual formulations, costing approximately 43% less in PPPY terms.

In addition to the cost benefits indicated above for each one of the proposed formulations, there are also potential freight savings associated with procuring fewer packs for scored tablets and for FDC. In addition, consolidation around a single product facilitates simpler management of country supply chains.

c. Please provide any additional relevant information with reference

Several of the suggested formulations are manufactured by a single company. The List of ARV Pharmaceutical Products from the Global Fund 2013 does not identify other manufacturers.¹

d. Is the product available in several low and middle income countries?

Yes

4. Assessment of public health need

a. Please provide the public health need for this product (1-2 sentences)

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UNAIDS reported in 2010 that 97% of the world’s 33.3 million people living with HIV/AIDS (PLHIV) were in low- and middle-income countries. In 2010 there were 2.7 million new HIV-1 infections and 1.8 million AIDS-related deaths. The 2011 WHO Progress Report for HIV/AIDS indicated that at the end of 2010 there were approximately 6.65 million people in low and middle income countries on antiretroviral therapy (47% of those eligible for therapy) but only 456,000 children on ART, a near 13.5 difference when compared to adults on treatment.

Despite progress in scaling-up prevention of mother-to-child-transmission (PMTCT), an estimated 390,000 children were infected with HIV in utero and during breastfeeding in 2010. Currently, over 90% of the world’s HIV-infected children live in sub-Saharan Africa, and of those eligible for treatment, only 23% were receiving antiretroviral therapy (ART) at the end of 2010.

Scaling-up treatment of paediatric HIV-1 infection in resource-limited settings is challenging for a number of reasons, especially due to the lack of access to antiretrovirals (ARVs) that are suitable for children, and facilitate treatment access and improve adherence, such as fixed-dose combinations (FDCs) that are both dispersible and neutral or pleasant tasting.

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

See table

5. Are there special requirements for use or training needed for safe/effective use?
If yes, please provide details in 1-2 sentences

None additional than those required for other formulations of the same medications.

6. Is the proposed product registered by a stringent regulatory authority?
   Yes No

See table

7. Any other comments
Even if these applications are for the inclusion of new formulations or specifying dispersibility for an existing medication in the EML, they should have included the references to the articles mentioned in the applications. Prices and cost-effectiveness data do not specify sources.

Several of these formulations are manufactured by a single company. Given the need of these medications and formulations in the paediatric population, it would be necessary to plan for scaled up manufacture of the recommended formulation to meet the increase in demand.

Based on the global need to improve availability of treatments for children with HIV, these applications are critical to ensure access to care.

8. What is your recommendation to the committee (please provide the rationale)

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## 19th Expert Committee on The Selection and Use of Essential Medicines

Summary of applications for new/modified formulations for HIV medicines in the WHO EML (children):

<table>
<thead>
<tr>
<th>Medication</th>
<th>Proposed formulation</th>
<th>Strength</th>
<th>If included in WHO EML(c) Section and formulation</th>
<th>WHO Guidelines</th>
<th>Regulatory authority</th>
<th>Expert recommendation</th>
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<tr>
<td><strong>Abacavir (ABC)</strong></td>
<td>Tablet (dispersible)</td>
<td>60mg</td>
<td>6.4.2.1 Nucleoside/Nucleotide reverse transcriptase inhibitors (antiretrovirals) Oral liquid: 100 mg (as sulfate)/5 mL. Tablet: 300 mg (as sulfate).</td>
<td>WHO Guidelines recommend ABC as an alternative nucleoside reverse transcriptase inhibitors (NRTI) in first-line ART in children. WHO-IATT Paediatric Working Group includes the dispersible formulation of ABC 60mg as “Optimal” for paediatric treatment of HIV on its Optimized Paediatric ARV List.</td>
<td>Approved by FDA in 1998 for adult and paediatric use in combination anti-HIV therapy. Abacavir sulphate 60mg dispersible tablets were added to the WHO list of pre-qualified (PQ) products on 20 August, 2010.</td>
<td>Include Abacavir (60mg) dispersible tablet formulation in the EML(c), restricted to children more than 3 months of age.</td>
</tr>
<tr>
<td><strong>Efavirenz (EFV)</strong></td>
<td>Tablet (scored)</td>
<td>200 mg, split 100 mg doses</td>
<td>6.4.2.2 Non-nucleoside reverse transcriptase inhibitors (antiretrovirals) Capsule: 50 mg; 100 mg; 200 mg. Oral liquid: 150 mg/5 ml. Tablet: 600 mg.</td>
<td>WHO Guidelines recommend efavirenz as an alternative NNRTI in first-line ART in children or as the preferred NNRTI for children older than three years and greater than 10kg on treatment for tuberculosis. WHO - IATT Pediatric Working Group includes the scored tablet formulation of EFV 200mg as “Optimal” for pediatric treatment of HIV on its Optimized Pediatric ARV List.</td>
<td>Efavirenz 200mg scored tablets were added to the WHO list of preapproved products on 14 May, 2008. Tentative approval by the FDA on 12 February, 2010.</td>
<td>Include scored tablet formulation of Efavirenz 200mg split into 100mg doses in the EML(c).</td>
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<td>Zidovudine + Lamivudine (AZT + 3TC)</td>
<td>Tablet (dispersible)</td>
<td>60 mg + 30 mg</td>
<td>6.4.2.3 Fixed dose combinations (protease inhibitors) Tablet: 30 mg + 60 mg; 150 mg + 300 mg.</td>
<td>WHO Guidelines recommend AZT+3TC as a preferred NRTI-backbone for infants and children.</td>
<td>WHO granted generic dispersible versions of AZT + 3TC prequalified status on 29 September 2011</td>
<td>Modify current entry in WHO EML(c) for a dispersible tablet formulation for Zidovudine + Lamivudine fixed dose combination</td>
</tr>
<tr>
<td>Stavudine + Lamivudine (d4T + 3TC)</td>
<td>Tablet (dispersible)</td>
<td>6 mg + 30 mg</td>
<td>Not included as a FDC but as individual medications in 6.4.2.1 (nucleoside / nucleotide reverse transcriptase inhibitors) Stavudine: Capsule: 15 mg; 20 mg; 30 mg. Powder for oral liquid: 5 mg/5 mL Lamivudine: Oral liquid: 50 mg/5 mL Tablet: 150 mg. A triple drug fixed-dose combination tablet of d4T/3TC/NVP in pediatric and adult strengths is included in the FDC section.</td>
<td>WHO Guidelines recommend d4T + 3TC for the treatment of HIV infection in all infants and children with no age restrictions.</td>
<td>Tentative approval by the FDA on June 2008 for PEPFAR. WHO granted generic versions of d4T+3TC dispersible tablets prequalified status on 8 Feb 2011.</td>
<td>Include the dispersible tablet formulation of Stavudine /Lamivudine 6mg/30mg for treatment of HIV-1 infection among children in both the EML and the EML(c).</td>
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<tr>
<td>Lamivudine + Nevirapine + Zidovudine (see note)</td>
<td>Tablet (dispersible)</td>
<td>30 mg + 50 mg + 60 mg</td>
<td>6.4.2 Fixed dose combinations</td>
<td>WHO Guidelines for HIV-infected infants and children The Zidovudine/ Lamivudine/ Nevirapine 60mg/30mg/50mg dispersible tablet is indicated for the treatment of HIV infection in children weighing &gt;3kgs.</td>
<td>Tentative approval by the FDA on July 2010 as part of PEPFAR.</td>
<td>Specify dispersibility for Lamivudine + Nevirapine + Zidovudine for this fixed dose combination in the EML(c).</td>
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<tr>
<td>Nevirapine (NVP)</td>
<td>Tablet (dispersible)</td>
<td>50 mg (as hemihydrates)</td>
<td>6.4.2.2 Non-nucleoside reverse transcriptase inhibitors (antiretrovirals) Oral liquid: 50 mg/5 ml Tablet: 200 mg.</td>
<td>WHO Guidelines recommend NVP as one of the preferred NNRTI in first-line ART therapy in children WHO IATT Pediatric Working Group includes the dispersible formulation of NVP 50mg as “Optimal” for pediatric treatment of HIV.</td>
<td>Tentative approval by the FDA on December 2005 as part of PEPFAR.</td>
<td>A low dose tablet would enable accurate dosing for infants and young children. Include 50mg dispersible tablet in the EML (c).</td>
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Note: Lamivudine + Nevirapine + Zidovudine is available only in dispersible formulation. The EML(c) does not specify the dispersibility for this FDC. The application is requesting the Expert Committee to specify the dispersibility.