A.1 Abacavir + dolutegravir + lamivudine – EMLc

Reviewer summary

☒ Supportive of the proposal

☐ Not supportive of the proposal

Justification (based on considerations of the dimensions described below):

- **Public health prevalence**

1. **In 2023 1.4 million children 0-14 years of age are living with HIV infection**, an estimated **120,000 new pediatric infections** occurred and 76,000 children died from AIDS-related causes.
2. **High prevalence of previously first-line ARV resistance in ART-naïve infants**: NNRTI-based ART has been widely used in pediatric patients for both prevention of transmission and treatment. However**, the 2021 WHO Report confirms high rates of NNRTI resistance among newly diagnosed infants, with a pooled prevalence of 45.5%**. In addition, pretreatment resistance to ABC and 3TC (the preferred NRTIs for pediatric patients) was also high and had exceeded 10% in five and four of the 10 reporting countries, respectively.

- **Evidence of comparative efficacy and safety**

1. Clinical trials

1) **In IMPAACT P1093 study** (single-arm, open-label trial) sponsored by NIH, **75 study participants aged 1-214 months received** the currently approved dose (determined by weight and age) o**f DTG film-coated tablets or dispersible tablets plus 2 NRTIs, 42 (56%) received DTG for at least 48 weeks,** of whom, 80% of participants were treatment-experienced, but all were INSTI-naïve**. At Week 48, (1) 69% of participants** achieved **HIV RNA <50 copies/mL and 79%** achieved **HIV RNA <400 copies/mL. (2) The median CD4 count (%) increase** from baseline to Week 48 was **141 cells/mm3 (7%). (3) The safety profile was comparable to that observed in adults, and both formulations were well tolerated by pediatric patients. (4) The effectiveness was comparable to that of treatment-experienced adult subjects.**

2) **In ODYSSEY trial** conducted by PENTA, **707 children aged <18 years (**weighing at least 14 kg) were enrolled**; 350 were on DTG treatment and 357 participants received the local SOC treatment.** Across all arms, **65% of participants received ABC/3TC** as their NRTI backbone. **Through 96 weeks, (1) 47 (13.4%) children receiving DTG experienced clinical or virologic treatment failure compared to 75 (21.0%) receiving SOC (adjusted HR for treatment failure 0.60 (95% CI, 0.42 to 0.86)** with treatment effects similar between first- and second-line cohorts**. (2) None of children failing first-line DTG therapy had a major DTG-related resistance mutation** while **29 (38.7%) children failing SOC developed NNRTI and/or NRTI resistance mutations. (3) Participants receiving DTG-based treatment were observed to have slightly increased weight, height, and BMI-for-age compared to those receiving SOC. (4) Similar rates of grade 3 or 4 adverse events and serious adverse events** occurred in participants receiving either DTG or SOC**. <u>Overall, the DTG-based regimens were concluded to be superior to SOC treatment in terms of efficacy in children weighing at least 14 kg with no substantive safety issues identified.</u>**

3) **IMPAACT 2019 trail study** evaluated ViiV's TRIUMEQ PD as a tablet for oral suspension**. 57 infants and children < 12 years and weighing 6 kg-<40 kg were enrolled (54 treatment-experience, 3 treatment- naïve).** Overall, **pharmacokinetic targets were achieved in all weight bands confirming the selected doses and safety criteria were met through 24 weeks of dosing. After 24 weeks, 52 (91%) participants were virologically suppressed. Overall adherence, acceptability and palatability were considered favorable.** None of adverse events were related to study drug and led to discontinuation.

2. Real-world studies showed the safety, effectiveness and better adherence of **DTG-based ART** for CLHIV children.

1) In a 2022 **real-world cohort study,** Mozambique introduced pDTG in children <=9 years of age across country and **all children from 4 weeks of age and weighing < 20 kg (3kg-19.9kg)** regardless their ART regimen or viral load, **were recommended to switch to or initiate ART with ABC/3TC+ pDTG**. Records of 1353 eligible CLHIV were reviewed and **1146 (84.7%) were** transitioned to or initiated **ABC/3TC+pDTG**. Most of the eligible children were treatment experienced but after at least 5 months post transition, **3/4 were virally suppressed**.

2) **In the TORPEDO study** (conducted in Benin, Nigeria, and Uganda)**,** most healthcare workers noted **an improvement in weight gain and adherence due to DTG's enhanced palatability**

	and ease of administration. The proportion of virologic suppression increased by 18%-25% after 6 months of switching to DTG-based ART. ➢ **Cost and cost-effectiveness considerations** 1. CHAI and Unitaid negotiated **ceiling prices** with Aurobindo and Mylan/Viatris of **US$15.00 per 180-count pack (EXW) of pADL**. 2. Although pADL represents a **slight increase in PPPY costs** from separate ABC/3TC (120/60mg) dispersible/scored tablets and DTG (10mg) dispersible/scored tablets, it is anticipated that **the price of pADL will decrease as volumes increase.** ➢ **Any other issues that may be relevant in determining the status of a medicine as 'essential'** (e.g., recommendations in WHO guidelines, feasibility of use, diagnostic requirements, availability, access). 1. **The 2021 WHO guidelines identify pADL as a preferred regimen for first-line therapy in pediatric HIV-infected patients from 4 weeks of age and older weighing at least 6 kg** for which dosing recommendations and a formulation are available. Recently, dose recommendations encompassing all pediatric patients older than 4 weeks and at least 3 kg for pADL have been endorsed by the WHO Paediatric Antiviral Working Group based on recently presented modeling and simulation work. 2. **Specialized testing is not required for patient diagnosis or management in African sites while receiving pADL therapy.** 3. **ABC/DTG/3TC 60/5/30 mg (TRIUMEQ PD) tablets for oral suspension (ViiV Healthcare)** are **approved for treatment of HIV in children** at least 3 months of age and weighing at least 6 kg **in the US, the EU, UK, Switzerland, and Chile**. ViiV Healthcare has approvals for TRIUMEQ PD from the FDA, the European Commission/EMA, and the WHO Prequalification program. 4. Two generic manufacturers of pADL (in India) were granted tentative approval by FDA in Aug 2023. Generic manufacturers are currently in the process of registering with local national drug regulatory authorities. **Generic pADL is currently being procured and introduced in LMIC, thanks to licensing agreements between ViiV Healthcare and the Medicines Patent Pool (MPP**). With three approved generic suppliers, and more in the regulatory pipeline, no anticipated supply challenges are anticipated. **Recommendation:** High rates (45%) of resistance to the previously recommended first-line ARV prompted **WHO to recommend rapid transition to DTG-based treatment for pediatric patients** in 2018 as child-friendly formulations become available. DTG has a favorable safety profile, a high barrier to emergence of resistance, and an acceptable level of drug-drug interactions. Moreover, **the DTG-based regimens were superior to SOC treatment in terms of efficacy in children weighing at least 14 kg with favorable safety and better tolerated, and the effectiveness was comparable to that of treatment-experienced adult patients**. The 2021 WHO consolidated HIV treatment guidelines recommends **ABC + 3TC + DTG as the preferred initial ARV regimen in infants and children**. Today the availability of **pADL** as a three-ARV, complete regimen, dispersible tablet provides preferred first-line treatment in **a convenient, palatable formulation** with WHO dosing recommendations for children from 4 weeks of age. As a complete regimen FDC, **the use of pADL is expected to improve patient adherence and also streamline procurement, prescribing, and dispensing.** I acknowledge the necessity of including pADL as an FDC in the EMLc. Meanwhile, I have some concerns about the price setting and regional accessibility and availability given that only originator **pADL** is available so far. On the other hands, three approved generic suppliers may not be enough to meet all supply needs across the countries. Despite these concerns, I believe listing child-friendly pADL as essential medicine is consistent with the WHO guideline recommendation, and will significantly improve the health of children living with HIV. Thus, **I recommend inclusion of abacavir/dolutegravir/lamivudine 60 mg/5 mg/30 mg (pADL), as a fixed dose combination (FDC), in the WHO EMLc.**
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**)	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable

(e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)	
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)	☒ Yes ☐ No ☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?	☒ Yes ☐ No ☐ Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable The treatment of paediatric patients with HIV infection is expected to be lifelong. Monitoring long-term safety and DGT resistance is needed.
Are there any issues regarding price, cost-effectiveness and budget implications in different settings?	☐ Yes ☒ No ☐ Not applicable
Is the medicine available and accessible across countries? (e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes)	☐ Yes ☒ No ☐ Not applicable
Does the medicine have wide regulatory approval?	☐ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☒ No ☐ Not applicable