F.6	Dolutegravir 10mg Scored Dispersible Tablets on the WHO Model List of Essential Medicines for Children
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments:
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.	The application is requesting for the inclusion of DTG 10mg scored dispersible tablets in the EMLc as a single-component product in the 'Antiretrovirals' category (6.4.2), in the sub-category: 'Integrase inhibitors' (6.4.2.4) without a square box. There are other integrase inhibitors listed for the treatment of HIV (e.g. raltegravir), but these are not considered therapeutic equivalents. This newly tentatively approved scored dispersible tablet formulation provides accurate dosing for infants and children as an easy-to-administer formulation that can either be dispersed in a small amount of water or taken directly by mouth. Dolutegravir (DTG), as a representative of the integrase inhibitor class of antiretroviral drugs (ARVs), has demonstrated superior effectiveness in multiple patient populations, a favorable safety profile, a high barrier to emergence of resistance, and an acceptable level of drug-drug interactions, making it an excellent candidate for use in a public health approach to HIV treatment. • In pediatric patients, DTG can be given with the dual nucleoside backbone of abacavir plus lamivudine which is available as a dispersible fixed dose combination product (FDC) and has been widely used globally in pediatric first line treatment. DTG represents a best-in-class HIV integrase strand transfer inhibitor (INSTI) in adult patients with HIV. Numerous clinical trials conducted around the world demonstrate that DTG is superior to EFV, raltegravir, and darunavir/ritonavir. These trials were gender balanced and included a broad range of ethnicities to account for most pharmacogenetic interactions.
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:

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). NNRTI-based ART has been widely used in pediatric patients for both prevention of transmission and treatment, and a recent survey of newly diagnosed children in five sub-Saharan African countries indicates resistance to one or more NNRTIs was identified in up to 53% of the cohort.10 These increasing rates of resistance to the previously recommended first-line ARV have prompted WHO to recommend rapid transition to DTG-based treatment as child-friendly formulations become available. Regulatory and normative bodies including the WHO (and its pediatric working groups) and the U.S. Food and Drug Administration (FDA) have accepted the concept of extrapolation of efficacy of ARVs in pediatric patients based on bridging pharmacokinetic (PK) data and supporting safety information. Thus, the most recent WHO treatment guidelines for pediatric use of DTG are based primarily on aligning PK data collected in children receiving DTG in clinical trials to adult PK targets. As a result, adolescents and older children are increasingly receiving DTG-based therapy using adult formulations found to be highly effective. Approval of the DTG 10mg scored, dispersible tablets will allow use of regimens considered optimal in both high- and low-income settings across all pediatric age groups. Clinical evidence of effectiveness in children is based on information gathered from literature search and review of WHO treatment guidelines and briefing documents and additionally supported by review of the U.S. FDA package insert for TIVICAY/TIVICAY PD (dolutegravir sodium, tablets and tablets for oral suspension, ViiV Healthcare), and review of the U.S. FDA Clinical Review of TIVICAY PD. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? Yes
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: From the data presented, DTG was shown to be safe and well tolerated, such that it can be administered in settings where laboratory monitoring is performed infrequently because of access or cost. Although there is limited clinical experience globally with use of DTG in younger children, it is recommended in this population based on extrapolation of efficacy from the larger, more diverse adult studies. In treatment-naïve adults, patients receiving DTG had an acceptable, low rate of treatment discontinuation due to adverse reactions (2%), compared to those receiving either RAL (2%) or efavirenz (10%). The most common adverse drug reactions noted in the TIVICAY (ViiV Healthcare) package insert of at least moderate intensity were insomnia, headache, and fatigue. More adverse reactions were mild and had little impact on treatment outcomes

Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Favourable
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Quality is high
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: While receiving DTG as part of an antiretroviral therapy (ART) regimen, patients should be monitored for treatment failure according to national guidelines. However, specialized testing is not required for patient diagnosis or management while receiving DTG-based therapy. HIV requires life-long treatment.
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.	The PPPY cost of DTG 10mg dispersible and scored tablets is less than US $40 (for a child between 10 and 13.9kg), which is significantly lower than other products currently used. In December 2020, CHAI, Viatris, Macleods, and Unitaid announced a pricing agreement for pediatric DTG 10mg scored, dispersible tablets. Under the agreement, Viatris and Macleods agreed to make generic pediatric DTG 10mg scored, dispersible tablets available at a price of US$36.00 PPPY for a child between 10 and 13.9kg (or US$4.50 per pack). This announcement means a significantly lower cost for yearly pediatric HIV treatment from over $480 per child to under $120 per child
Any additional comments	None
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.	Formulations for pediatric use are essential in the management of HIV/AID. This formulation (dispersible tablets) are timely. I recommend to the committee to accept this application
References (if required)	