Application for Inclusion of Dolutegravir (DTG) 10mg Scored Dispersible Tablets on the WHO Model List of Essential Medicines for Children (EMLc)

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General Information

1. Summary statement of the proposal for inclusion, change or deletion.

This document proposes the inclusion of dolutegravir (DTG) 10mg scored dispersible tablets for treatment of HIV-1 infection among pediatric patients (at least 4 weeks of age and weighing at least 3kg) living with HIV/AIDS on the core list of the Model List of Essential Medicines for Children (EMLc). DTG 50mg film coated tablets are currently included in the WHO Model List of Essential Medicines (EML) and the EMLc for treatment of HIV in adults and pediatric patients weighing at least 25kg. This application proposes to add the newly approved dispersible tablet formulation (also called tablets for oral suspension) to span the pediatric ages and weight bands requiring a lower dose or more child-friendly formulation.

The principal reasons for requesting this inclusion are as follows:

- 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.
- According to the most recent WHO HIV Interim Guidelines (Updated Recommendations on First-Line and Second-Line Antiretroviral Regimens and Post-Exposure Prophylaxis and Recommendations on Early Infant Diagnosis of HIV), a DTG-based regimen is recommended as a preferred first-line regimen for pediatric patients for whom dosing recommendations and an appropriate formulation are available.[1]
- 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.

2. Relevant WHO technical department and focal point (if applicable).

Martina Penazzato, WHO/HTM/HIV/ATC

3. Name of organization(s) consulted and/or supporting the application.

Clinton Health Access Initiative, Inc.

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

INN: Dolutegravir

ATC: Dolutegravir J05AX12

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

Each tablet contains dolutegravir 10mg as a dispersible tablet with a functional score.

FDA tentatively-approved manufacturers:

- Viatris Inc. (formerly Mylan Laboratories Limited)
  Plot No. 564/A/22
  Road No. 92
  Jubilee Hills, Hyderabad – 500096, India

Currently under review by FDA and WHO Prequalification Team

- Macleods Pharmaceuticals
  Atlanta Arcade, Marol Church Road
  Near Hotel Leela, Andheri East 400059
  Mumbai India

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

We request 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.

Treatment details, public health relevance and evidence appraisal and synthesis

7. Treatment details (requirements for diagnosis, treatment and monitoring).

The most recent WHO recommendations for treatment of HIV in infants and children identify DTG as a preferred drug for first line therapy in all ages for which dosing recommendations and a formulation are available. This recommendation pre-dated the availability of a child-friendly DTG formulation but can now be widely applied across ages and weight bands. DTG should be given together with 2 nucleoside reverse transcriptase inhibitors (NRTIs) appropriate for pediatric patients (abacavir plus lamivudine or zidovudine plus lamivudine). In addition, the WHO 2018 interim guidelines also recommend that DTG in combination with an optimized NRTI backbone is the preferred second-line regimen for children with approved DTG dosing for whom non-DTG-based regimens are failing.

Dosing recommendations for DTG 10mg scored dispersible tablets are currently available for infants and children 4 weeks of age and older and 3kg and heavier (see Table 1). Because the dispersible tablets are more bioavailable than the previously approved film coated tablets, 30mg given as 3x10mg dispersible tablets provides similar drug exposure as 50mg given as 1 adult/adolescent strength film coated tablet. U.S. pediatric treatment guidelines also recommend use of dispersible tablets[2] (a 5mg dispersible tablet is approved for use in the US) in pediatric patients and these recommendations are aligned with those endorsed by the WHO.

Table 1: Recommended Dosage of Dolutegravir Tablets for Oral Suspension in Pediatric Patients 4 Weeks and Older Weighing at least 3 kg

Body Weight	Dolutegravir Tablets for Oral Suspension	
	Daily Dose[a]	Number of 10-mg Scored Tablets
3 kg to less than 6 kg	5 mg once daily	½
6 kg to less than 10 kg	15 mg once daily	1 ½
10 kg to less than 14 kg	20 mg once daily	2
14 kg to less than 20 kg	25 mg once daily	2 ½
20 kg and greater[b]	30 mg once daily	3

[a] If certain UGT1A or CYP3A inducers are coadministered, then administer dolutegravir tablets for oral suspension twice daily.

[b] Dosing for pediatric patients weighing 20 kg and greater may follow the adult recommendations using dolutegravir 50 mg tablets.

HIV infection can be diagnosed with relatively simple, point-of-care, rapid testing kits or in clinic or hospital laboratories. The WHO recommends treatment for all patients diagnosed with HIV infection regardless of age, clinical stage, or laboratory parameters. 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.

8. Information supporting the public health relevance.

In its 2020 AIDS Update, UNAIDS reported there were 38 million people living with HIV/AIDS globally, 1.7 million new HIV-1 infections, and 690,000 thousand HIV-related deaths, a decrease of 23% since 2010. Over 95% of infected people live in low and middle-income countries (LMIC) with inadequate resources to effectively combat the epidemic. While some countries have achieved declines in new HIV infections among adults of 50% or more, global data show that many others have not made measurable progress and some areas in Eastern Europe, central Asia, northern Africa and Latin America have experienced concerning increases in new HIV infections. Overall, approximately 25.4 million people were receiving antiretroviral therapy (ART) in 2019, an estimated two thirds of HIV infected people.[3]

Early and effective ART not only significantly improves the health of those living with HIV, but also reduces transmission of the disease as shown in the START study.[4] For this reason, beginning in 2015, the WHO called for treatment for all people with HIV. Easy to administer, highly effective, safe treatment options remain desperately needed in many areas of the world.

However, the numbers of new infections, deaths, and number of patients on treatment missed the UNAIDS 90-90-90 targets, which called for 90 percent of people living with HIV to know their status, 90 percent of those with known infection to be on ART, and 90 percent of those on ART to be virally suppressed by the year 2020.[5] In spite of missing these 2020 targets, the 2020 UNAIDS Update noted that the introduction of dolutegravir was associated with rapid viral suppression. Improvement in outcomes compared to other regimens was noted in both adults and in boys and girls 0-14 years of age who made up an estimated 13% of new HIV diagnoses in sub-Saharan Africa. [2]

UNAIDS estimates that since 2010, 1.4 million pediatric HIV infections have been averted by ARTs for the prevention of mother to child transmission of HIV, a dramatic reduction. Despite this impressive reduction in mother to child transmission of HIV in recent years, 150,000 new pediatric infections occurred in 2019 (children 0-14 years of age)[2] and there are an estimated 1.8 million children living with HIV, the vast majority in sub-Saharan Africa. Evidence shows that in the absence of ART, over 50% of HIV-infected infants progress to AIDS or death by the age of 2 years[6], but the introduction of effective pediatric ART has changed HIV infection in children from a life-threatening illness to a chronic-but-manageable infection, albeit highly dependent on good adherence. Despite recognition of the advantages of early treatment, pediatric treatment coverage still reached only 53% of children eligible for treatment in 2019 (estimated 950,000)[2] and data consistently show children are less likely than adults to achieve viral suppression. [7]

Recent years have seen the development of a variety of dosage forms for pediatric ARVs but, compared to the demand for adult ARVs, children account for just 5% of patients on ART, thereby rendering the global pediatric market smaller and more vulnerable to supply disruption. The Optimal Pediatric ARV Formulary and Limited-use List was first developed in 2011 to address this challenge. It provides guidance to streamline the selection of pediatric ARV dosage forms to those that conform to a list of criteria, including dosing flexibility, child-friendly to take and caregiver-friendly to administer, optimization of supply chain management, and availability of quality assured products in resource limited settings. The Optimal Formulary is revised on a regular basis to reflect current WHO recommended regimens, most recently in December 2020, when it was revised to include DTG 10mg scored dispersible tablets as preferred first line therapy for children needing lower dosing or unable to swallow tablets.[8]

Recent surveys of HIV resistance in patients initiating ARVs suggest that the prevalence of pre-treatment drug resistance to efavirenz (EFV) and nevirapine, both non-nucleoside reverse transcriptase inhibitors (NNRTIs), has significantly increased since 2001, as ART coverage has expanded in LMIC. In WHO's national survey of pre-treatment resistance conducted in 2014–2016, NNRTI resistance among adults initiating first-line therapy with no prior ARV exposure was 8.3% but it was significantly higher among individuals initiating first-line therapy after some prior ARV drug exposure (21.6%). Six of 11 countries in the WHO survey reported >10% prevalence of pre-treatment resistance to NNRTIs but prevalence of NNRTI resistance among patients receiving treatment may be significantly higher (47-89% of those without viral suppression).[9] 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.

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.[11,12,13] These trials were gender balanced and included a broad range of ethnicities to account for most pharmacogenetic interactions. DTG was also 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. 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.

9. Review of benefits: summary of evidence of comparative effectiveness.

- *Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)*

  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)[14], and review of the U.S. FDA Clinical Review of TIVICAY PD.[15]

- *Summary of available data (appraisal of quality, outcome measures, summary of results)*

  As noted above, DTG has been shown to be effective in diverse adult patient populations enrolled in multiple clinical trials conducted internationally. The results of these adult clinical trials were reviewed in the dossier submitted in 2016 to support inclusion of DTG 50mg as first-line ART in the EML and will not be reiterated in this dossier. DTG-based regimens are now widely used in the U.S. and Europe and has become the first line therapy for HIV in LMIC as the tenofovir/lamivudine/ dolutegravir (TLD) FDC becomes more widely available.

  The pediatric data presented and published to date and used to support approval of the innovator's dispersible tablet is comprised of two ongoing clinical trials. The trials on which WHO treatment and dosing recommendations are based include the same two ongoing studies, the IMPAACT P1093 study, sponsored by the U.S. National Institutes of Health, and the ODYSSEY study, sponsored by the Paediatric European Network for Treatment of AIDS (PENTA). PK, safety, and efficacy data from these trials have been reported and reviewed sequentially as new weight band cohorts have been completed. Both trials evaluated pediatric patients down to 4 weeks of age and 3kg using a combination of dispersible tablets and film-coated tablets depending on study participants' age, weight, and ability to swallow tablets. Although complete clinical data from the ODYSSEY study was not available, some data were provided to regulatory agencies to support registration of the innovator's dispersible tablet. There is currently no data to support dosing in infants less than 4 weeks of age (neonates) or in pre-term infants.

  IMPAACT P1093 is an ongoing single-arm, open-label trial of DTG in children with HIV. FDA's initial approval of dolutegravir for use in children weighing as low as 40 kg was based on data from 23 treatment-experienced, INSTI-naive adolescents.[16] These data have been previously described in an earlier dossier requesting addition of the DTG 50mg film coated tablets to the EMLc in 2019.

  Data from P1093 included Cohorts 1 (aged 12 years to < 18 years) and 2 (6 years to <12 years) which provided support for use of DTG film-coated tablets in pediatric patients $\geq$ 14 kg and Cohorts 3 (2 to < 6 years), 4 (6 months to < 2 years), and 5 (4 weeks to < 6 months) which provided evidence supporting use of DTG dispersible tablets. As the study progressed, dosing in some cohorts was adjusted to achieve the pharmacokinetic targets. Seventy-five study participants received the

currently approved dose (determined by weight and age) of DTG film-coated tablets or dispersible tablets. These 75 participants ranged from 1 to 214 months, 59% were female, and 68% were black or African American. Eighty percent of participants were treatment-experienced, but all were INSTI-naïve. Among these 75 patients who received either DTG film-coated tablets or DTG dispersible tablets according to the approved dosing recommendations for their weight band, 42 received DTG for at least 48 weeks. At Week 48, 69% of participants achieved HIV RNA <50 copies/mL and 79% achieved HIV RNA <400 copies/mL. The median CD4 count (percent) increase from baseline to Week 48 was 141 cells/mm^3 (7%). Overall, the safety profile in P1093 participants was comparable to that observed in adults and both formulations were well tolerated by pediatric patients. The effectiveness observed in the trial was comparable to that of treatment-experienced adult subjects.[14,17,18]

The ODYSSEY trial, conducted by PENTA, enrolled both treatment-naive and treatment-experienced pediatric patients in the European Union (EU), Thailand, and several African countries; this trial initially evaluated doses approved by the European Medicines Agency at the time the trial started. A total of 674 children aged <18 years were enrolled; 282 children started DTG as first-line therapy and 392 started DTG as second-line therapy.[19] Nested PK substudies within ODYSSEY also evaluated simplified pediatric dosing that aligned with WHO-recommended weight bands. PK data are available from a cohort of children weighing >25kg who switched to the DTG 5mg film-coated tablet.[20] Data from another ODYSSEY cohort reported on children weighing 20kg to <25kg who received either the DTG 50 mg film-coated tablet or 30mg of DTG administered as six 5mg dispersible tablets. Both of these doses achieved area under the curve (AUC) and C_{max} values that were higher than adult PK reference values, but still acceptable, and both doses achieved C_{trough} values that were similar to adult reference values, as was weight band dosing for infants and children less than 20kg.[21,22] Long-term safety and effectiveness assessments in the ODYSSEY trial are ongoing and final data through 96 weeks of dosing are expected in 2021.

DTG dosing in the ODYSSEY study for weight bands below 20kg was slightly different from that in P1093, primarily because P1093 was originally designed to dose by age rather than by weight band. Both studies contributed PK data to the registrational submissions for the innovator's dispersible tablet (TIVICAY PD®, dolutegravir 5mg tablets for oral suspension, ViiV Healthcare). Combined PK data from P1093 and ODYSSEY across all age/weight cohorts form the basis for the current FDA and WHO treatment recommendations and are summarized in Table 2. In addition, modeling and simulations that included UGT1A1 maturation in infants was used to support the dose of DTG down to 4 weeks of age and 3 kg.

Table 2: Summary of Pharmacokinetic Parameters in Pediatric HIV-1–Infected Participants (Pooled Analyses for IMPAACT P1093 and ODYSSEY[a] Trials)

Weight Band	Dose[b] of DTG FCT or DTG DT	n	Pharmacokinetic Parameter Geometric Mean (%CV)		
			C_{max} (mcg/mL)	AUC_{0-24h} (mcg·h/mL)	C_{24h} (ng/mL)
3 kg to <6 kg	5 mg DT once daily	8	3.80 (34)	49.37 (49)	962 (98)
6 kg to <10 kg	15 mg DT once daily	17	5.27 (50)	57.17 (76)	706 (177)

10 kg to <14 kg	20 mg DT once daily	13	5.99 (33)	68.75 (48)	977 (100)
14 kg to <20 kg	25 mg DT once daily	19	5.97 (42)	58.97 (44)	725 (75)
20 kg to <25 kg	30 mg DT once daily	9	7.16 (26)	71.53 (26)	759 (73)
≥20 kg	50 mg FCT once daily	49	4.92 (40)	54.98 (43)	778 (62)
Adults	50 mg FCT once daily	[c]	3.67 (20)	53.6 (27)	1110 (46)

[a] Data from 2 weight-band-based pharmacokinetic substudies in the ODYSSEY trial.
[b] The bioavailability of DTG tablets for oral suspension is ~1.6-fold that of DTG film-coated tablets.
[c] Adult pharmacokinetic data are based on population pharmacokinetic analyses from clinical trials.
DTG FCT, dolutegravir film-coated tablets; DTG DT, dolutegravir dispersible tablets
Source: US Food and Drug Administration. TIVICAY and TIVICAY PD Package Insert, June 2020.[14]

- *Summary of available estimates of comparative effectiveness*

  In the adult clinical studies to date, DTG-based regimens were either non-inferior or superior in efficacy to comparator regimens containing other integrase inhibitors, boosted protease inhibitors, and NNRTIs regardless of patient population. There are no comparative pediatric trials available but both the WHO working groups and multiple regulatory agencies (including the U.S. FDA and the EMA) endorse the concept of extrapolating efficacy from well-designed, adequately-powered adult trials on the basis of similar pharmacokinetic profile and supplemental safety data.

10. Review of harms and toxicity: summary of evidence of safety.

- *Estimate of total patient exposure to date*

  Since its approval in 2013, DTG has become a widely used anchor for ARV regimens around the world. The WHO estimated that as of 2017, around 300,000 adults living with HIV were receiving a DTG-based regimen in high income countries (HIC). Lower income countries such as Botswana, Brazil, and Kenya that were early to adopt DTG-based treatment were estimated to have 80,000, 60,000, and 13,000 patients, respectively, receiving the drug in 2017.[23] Use of DTG-based regimens have scaled up rapidly since then with an estimated 6 million adults and adolescents receiving these regimens. CHAI market analysis predicts that by the year 2022, DTG-based regimens (primarily as TLD) will account for almost 90% of the first line ARV market for adults and adolescents.[24] To date, there is little information regarding the number of younger children using DTG outside of clinical trials. Some relatively small cohorts in HIC have been reported, primarily to support safety (see below).

- *Description of the adverse effects/reactions and estimates of their frequency*

  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.

  The FDA Clinical Review of the data submitted to support registration of DTG dispersible tablets describes the safety data available from P1093 through 48 weeks of dosing. In P1093, 13 subjects

(17%) experienced adverse reactions attributed to DTG and all were assessed as Grade 1 or Grade 2 (mild or moderate). Adverse drug reactions reported in more than 1 study participant were decreased blood bicarbonate (n=3), decreased hemoglobin (n=2), decreased neutrophil count (n=4), and IRIS (n=2). In data evaluated by the FDA in support of the dispersible tablet registration, new adverse events occurred in 7 subjects (7%) in the ODYSSEY safety population (n=97) through Week 24. The only adverse event reported in more than 1 subject was anemia in 3 subjects (3%). The following adverse events occurred in only one subject each: neutropenia, diarrhea, hepatitis A, lower respiratory tract infection, measles, meningitis cryptococcal, otitis media, pneumonia, dehydration, and malnutrition. None of these AEs were thought to be related to study drug by the investigators.[15] The FDA package insert also notes that the adverse event profile in the pediatric cohorts of P1093 was similar to that observed in adults.[14]

In the original adult clinical trials, patients on DTG experienced significantly fewer incidences of nervous system disorders and psychiatric disorders than those receiving EFV, however, there have been post-marketing reports of neuropsychiatric events (such as insomnia or depression) among adults receiving DTG-based treatment since its approval. Causality for these events has been difficult to determine as many patients are reported to have a previous history of psychiatric symptoms.

In a surveillance study of birth outcomes among pregnant women on antiretroviral therapy in Botswana, an increased rate of neural tube defects was initially reported among infants born to women who were receiving DTG at the time of conception.[26,27] However, as the surveillance continued and included more women at more sites over time, the rate of these neural tube defects decreased and seems to have settled at about 0.2%, not statistically different from reference populations taking other ARV regimens.[28]

- *Summary of available data (appraisal of quality, summary of results)*

  Overall, the quality and quantity of data supporting the safety of DTG-based regimens in adults is good and includes both randomized clinical trials and observational cohorts in a variety of settings. The ongoing pediatric clinical trials have identified appropriate dosing down to 4 weeks of age and 3kg and FDA and WHO recommended dosing are aligned and supported by the registrational safety database.

- *Summary of comparative safety against comparators*

  A systematic review and meta-analysis conducted by the WHO concluded that among treatment-naive adults, treatment with an INSTI (particularly DTG) plus two NRTIs, had superior efficacy and tolerance to the current standard of care regimens of EFV plus two NRTIs and fewer discontinuations.[29]

- *Identification of variation in safety that may relate to health systems and patient factors*

  No specific safety issues associated with DTG are expected to pose a differential risk in the international health setting. However, the last remaining question on TLD use in children is in the population of patients who require concurrent treatment for tuberculosis. Clinical pharmacology/drug interaction studies conducted in adults suggest that a higher/twice daily dose of DTG may be appropriate in this group. Clinical trials are currently underway in HIV/TB coinfected children to assess PK, efficacy, and safety in the setting of TB treatment.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

DTG 10mg scored, dispersible tablets for patients 3-19.9kg

As illustrated in the table below, 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.

	DTG (10 mg) Tablets (Disp, Scored) - 90 Pack		LPV/r (40/10 mg) Oral Pellets/Granules - 120 Pack		LPV/r (100/25 mg) Tablets – 60 Pack	
Reference Price List	**Price/Pill***	**PPPY (10-13.9kg)**	**Price/Unit**	**PPPY (10-13.9kg)**	**Price/Pill**	**PPPY (10-13.9kg)**
Global Fund PPM, Oct 2020	$0.05	$36.50	$0.15	$444.08	$0.11	$118.64
GHSC-PSM, Nov 2020	$0.05	$36.50	$0.14	$404.54	$0.10	$108.41
Average	**$0.05**	**$36.50**	**$0.15**	**$424.31**	**$0.11**	**$113.53**

Prices in USD (EXW). Please note that the GHSC-PSM prices are not reference prices but represent the latest blended average pricing of actual procurement.

**Given recent approval of the product, DTG 10 mg price as referenced by Unitaid Press Release, December 1, 2020[30] as it has not been added to global reference price lists yet.*

Special Pricing Arrangements

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. While cost should not be the overriding consideration for treatment decisions, DTG 10mg scored, dispersible tablets will bring a dual benefit to programs in terms of quality and cost savings, as shown below.

Annual Estimated Cost of Treatment Comparison by Weight Band (USD, Ex-Works)

Product	3-5.9 kg	6-9.9 kg	10-14.9 kg	15-19.9 kg
ABC/3TC (120/60 mg Disp/Scored) + DTG (10 mg Disp./Scored)	$49.28	$87.60	$116.80	$146.00
ABC/3TC/LPV/r (60/30/40/10 mg) '4-in-1' Granules in Capsules	$182.50	$273.75	$365.00	$456.25
ABC/3TC (120/60 mg Disp/Scored) + LPV/r (40/10 mg) Pellets	$222.65	$333.98	$445.30	$556.63
ABC/3TC (120/60 mg Disp/Scored) + LPV/r (40/10 mg) Granules	$262.19	$393.29	$524.38	$655.48

Source: Unitaid Press Release, December 1, 2020[30]

Country Level Cost Effectiveness Analyses
At the time of submission, no known cost-effectiveness studies have been conducted for DTG scored, dispersible tablets for children.

Regulatory information

12. Summary of regulatory status and market availability of the medicine.

DTG 50mg tablets (Tivicay®, ViiV Healthcare) are approved for treatment of HIV in adults and adolescents in both the U.S., the E.U., and many other jurisdictions. At the time of the recent pediatric dispersible tablet review, the FDA revised dosing recommendations for the 50mg tablets to allow use in children down to 20kg. DTG 5mg tablets for oral suspension (TIVICAY PD®, ViiV Healthcare) are approved for infants and children 4 weeks of age and older and 3kg or more in the U.S. and the E.U. Registration of ViiV's tablets for oral suspension (also called dispersible tablets) is in progress in additional countries. License agreements for DTG have been made available by the innovator companies through the Medicines Patent Pool. In addition, ViiV, CHAI, Mylan (now Viatris, Inc), and Macleods Pharmaceuticals engaged in a novel partnership to expedite development of an optimized pediatric DTG formulation and bring it to market in LMICs.[31]

The optimal formulation to provide appropriate dosing for all age and weight bands was identified by the WHO-sponsored Paediatric Antiretroviral Drug Optimization (PADO) working group as a DTG 10mg scored dispersible tablet.[32] This formulation was added subsequently to the WHO Prequalification Expression of Interest list. The FDA granted the first generic version of DTG 10mg scored dispersible tablets (Mylan, Hyderabad) tentative approval on 19 November 2020. By virtue of the FDA tentative approval, Mylan's dispersible tablets will be cross-listed on the WHO List of Prequalified Medicinal Products. Not uncommon for pediatric formulations, there is currently a single supplier for DTG 10mg scored dispersible tablets, with another supplier's product (Macleods Pharmaceuticals, Mumbai) under review by both FDA and WHO Prequalification Team.

13. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).

Dolutegravir is included in the British Pharmacopoeia.

14. References: Comprehensive reference list and in-text citations.

1. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines, supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. World Health Organization, Geneva. December, 2018. https://apps.who.int/iris/bitstream/handle/10665/277395/WHO-CDS-HIV-18.51-eng.pdf?ua=1 with accompanying Annex 3: Dosages of ARV drugs. World Health Organization, Geneva. December, 2018. https://www.who.int/hiv/pub/guidelines/ARV_Guidelines-2018-Annex3.pdf?ua=1

2. Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Available at https://clinicalinfo.hiv.gov/sites/default/files/inline-files/pediatricguidelines.pdf. Accessed November 25, 2020.

3. Global AIDS Update 2020 – Seizing the Moment. UNAIDS. July 2020. https://www.unaids.org/sites/default/files/media_asset/2020_global-aids-report_en.pdf

4. The INSIGHT START Study Group. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *N Engl J Med* 2015;373(9):795-807.

5. 90–90–90 - An ambitious treatment target to help end the AIDS epidemic. UNAIDS. January 2017. http://www.unaids.org/sites/default/files/media_asset/miles-to-go_en.pdf

6. Newell ML, Coovadia H, Cortina-Borja M, et.al. "Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis." *Lancet.* 2004 Oct 2-8;364(9441):1236-43.

7. UNAIDS. Progress towards the Start Free, Stay Free, AIDS Free targets, 2020 report. https://www.unaids.org/sites/default/files/media_asset/start-free-stay-free-aids-free-2020-progress-report_en.pdf

8. World Health Organization. AIDS FREE Toolkit, "The 2020 Optimal Formulary and Limited-Use List for paediatric ARVs." 2020. https://www.who.int/hiv/pub/paediatric/aids-free-toolkit/en/

9. HIV drug resistance report 2017. Geneva: World Health Organization; 2017. http://apps.who.int/iris/bitstream/handle/10665/255896/9789241512831-eng.pdf?sequence=1

10. Jordan MR, Penazzato M, Cournil A, et.al. Human Immunodeficiency Virus (HIV) Drug Resistance in African Infants and Young Children Newly Diagnosed With HIV: A Multicountry Analysis. *Clin Infect Dis,* 2017; 65(12):2018–25.

11. Walmsley SL, Antela A, Clumeck N, et al. "Dolutegravir plus Abacavir–Lamivudine for the Treatment of HIV-1 Infection." *N Engl J Med* 2013; 369:1807-1818.

12. Raffi F, Jaeger H, Quiros-Roldan E, et al. "Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial." *Lancet Infect Dis* 2013; 13(11):927-35

13. Molina, Clotet B, van Lunzen J, et al. "Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study." *Lancet HIV*. 2015 Apr;2(4): e127-36.

14. U.S. Food and Drug Administration. TIVICAY and TIVICAY PD package insert. Revised June 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213983s000lbl.pdf

15. U.S. Food and Drug Administration. Clinical Review and Summary CDTL, Dolutegravir (TIVICAY and TIVICAY PD). June 2020.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213983Orig1s000MedR.pdf

16. Viani RM, Alvero C, Fenton T, et. al. "Safety, pharmacokinetics and efficacy of dolutegravir in treatment-experienced HIV-1 infected adolescents: 48-week results from IMPAACT P1093." *Pediatr Infect Dis J* 2015.

17. Wiznia A, Alvero C, Fenton T, et. al. "Abstract: IMPAACT 1093: dolutegravir in 6- to 12-year-old HIV-infected children: 48-week results." *23rd Conference on Retroviruses and Opportunistic Infections*. March, 2016, Boston, MA.

18. Ruel, T., E. P. Acosta, R. Singh, C. Alvero, T. Fenton, K. George, E. Townley, R. Hazra, S. Popson, A. M. Buchanan, C. Brothers, C. Vavro, A. Wiznia and IMPAACT P1093 Team. "Pharmacokinetic and 4-week safety/efficacy of dolutegravir (S/GSKI349572) dispersible tablets in HIV-infected children aged 4 weeks to <6 years: results from IMPAACT PI093." *International AIDS Conference*. July, 2018, Amsterdam, Netherlands.

19. Moore C, Kekitinwa A, Kaudha E, et.al. "Abstract: ODYSSEY: A randomised trial evaluating the efficacy and toxicity of dolutegravir-based antiretroviral therapy compared to standard of care in HIV-infected children starting first-line or second-line therapy: design, current status and baseline characteristics." *10th International Workshop on HIV Pediatrics,* 21- 22 July 2018, Amsterdam.

20. Turkova A, Bollen P, Kaudha E, et. al. "Abstract: Steady-state pharmacokinetics and early safety data in HIV-infected African children weighing ≥25kg after switching to 50mg film-coated dolutegravir tablets in the ODYSSEY trial." *10th International Workshop on HIV Pediatrics* 21- 22 July 2018, Amsterdam.

21. Bollen, P. D. J., C. L. Moore, H. A. Mujuru, S. Makumbi, A. R. Kekitiinwa, E. Kaudha, A. Parker, G. Musoro, A. Nanduudu, A. Lugemwa, P. Amuge, J. G. Hakim, P. Rojo, C. Giaquinto, A. Colbers, D. M. Gibb, D. Ford, A. Turkova and D. M. Burger. "Simplified dolutegravir dosing for children with HIV weighing 20 kg or more: pharmacokinetic and safety substudies of the multicentre, randomised ODYSSEY trial." *Lancet HIV* 2020. **7**(8): e533-e544. https://www.thelancet.com/action/showPdf?pii=S2352-3018%2820%2930189-2

22. Waalewijn, H., P. Bollen, C. Moore, A. Kekitiinwa, P. Amuge, H. Mujuru, E. Chidziva, V. Musiime, E. Kaudha, A. Lugemwa, A. Makumi, A. Violari, E. Variava, S. Ali, C. Giaquinto, P. Rojo, A. Colbers, D. Gibb, D. Ford, A. Turkova, D. Burger and The ODYSSEY Trial Team. 'Pharmacokinetics of dolutegravir 5mg dispersible tablets in children weighing 6 to < 20kg dosed using WHO weight bands.' *IAS Conference on HIV Science.* July 2019, Mexico City, Mexico

23. Dolutegravir (DTG) and the fixed dose combination (FDC) of tenofovir/lamivudine/dolutegravir (TLD): briefing note. World Health Organization. April 2018. http://www.who.int/hiv/pub/arv/DTG-TLD-arv_briefing_2018.pdf

24. HIV Market Report: The state of the HIV treatment, testing, and prevention markets in low- and middle-income countries, Issue 11, September 2020. Clinton Health Access Initiative.
https://3cdmh310dov3470e6x160esb-wpengine.netdna-ssl.com/wp-content/uploads/2020/09/2020-CHAI-HIV-Market-Report.pdf

26. Zash R, Holmes L, Makhema J, et al. "Surveillance for neural tube defects following antiretroviral exposure from conception." Presented at: *22nd International AIDS Conference*. 2018, Amsterdam, Netherlands. Available at: http://www.natap.org/2018/IAC/IAC_52.htm.

27. Zash R, Makhema J and Shapiro RL. "Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception." *N Engl J Med* 2018;379(10): 979-981.

28. Zash, R., Holmes L, Disego M, et al. "Update on neural tube defects with antiretroviral exposure in the Tsepamo study." Presented at *AIDS2020 Virtual*, July 2020. https://cattendee.abstractsonline.com/meeting/9289/presentation/3500

29. Kanters S, Vitoria M, Doherty M, et al. "Comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection: a systematic review and network meta-analysis." *Lancet HIV*. 2016; 3: e510–20.

30. Unitaid Press Release, "Groundbreaking Agreement Reduces by 75% the Cost of HIV Treatment for Children in Low-and Middle-Income Countries." December 1, 2020. https://unitaid.org/news-blog/groundbreaking-agreement-reduces-by-75-the-cost-of-hiv-treatment-for-children-in-low-and-middle-income-countries/#en

31. ViiV Healthcare. Press release, "Innovative public-private partnership initiative to accelerate development of optimal pediatric formulations of dolutegravir to improve the lives of CLHIV." July 2018. https://viivhealthcare.com/en-gb/media/press-releases/2018/july/innovative-public-private-partnership-initiative-to-accelerate-development-of-optimal-pediatric-formulations-of-dolutegravir-to-improve-the-lives-of-clhiv/

32. World Health Organization. Paediatric Antiretroviral Drug Optimization (PADO) Meeting 4, *Meeting report. 10-12 December 2018, Geneva, Switzerland.* https://www.who.int/hiv/pub/meetingreports/paediatric-arv-optimization-pado4/en/