Dolutegravir

Essential medicine status ✓

EMLc | ATC codes: J05AJ03

Indication	Human immunodeficiency virus disease without mention of associated disease or condition, clinical stage unspecified ICD11 code: 1C62.Z
INN	Dolutegravir
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid:** 50 mg tablet ; 10 mg tablet (dispersible, scored) (EMLc)
EML status history	First added in 2017 (TRS 1006) Changed in 2019 (TRS 1021) Changed in 2021 (TRS 1035)
Sex	All
Age	Also recommended for children
Age restriction	10 mg dispersible tablet: ≥ 4 weeks
Weight restriction	50 mg tablet: ≥ 25 kg / 10 mg dispersible tablet: ≥3 kg
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Dolutegravir
DrugBank	Dolutegravir

Expert Committee recommendation

The Expert Committee recognized that age-appropriate, child-friendly formulations of antiretroviral medicines, when available and quality-assured, are essential to meet the needs of paediatric patients with HIV. The Committee noted evidence that dolutegravir-based regimens show superiority over NNRTI plus protease inhibitor regimens in paediatric patients and that the dolutegravir-based regimens have been recommended in WHO guidelines as the preferred first-line therapy in infants and children aged 4 weeks and older, for which dosing recommendations and age-appropriate formulations are available. The Committee therefore recommended the inclusion of the new formulation of dolutegravir 10 mg dispersible tablets to the core list of the EMLc for the treatment of children 4 weeks of age and older and weighing at least 3 kg. The Committee noted however that the 10 mg dispersible tablet formulation and the 50 mg film-coated tablet formulation of dolutegravir have not been shown to be bioequivalent and should not be used interchangeably in patients on a milligram-to-milligram basis.

Background

Dolutegravir 50 mg tablets were added to the core list of the EML in 2017 for treatment of adult patients with HIV-1 infection in combination with an optimized nucleoside reverse-transcriptase inhibitor (NRTI) background (1). In 2019, dolutegravir 50 mg tablets were added to the core list of the EMLc for treatment of paediatric patients with HIV-1 weighing 25 kg or more, in combination with an optimized NRTI background, in line with recommendations in WHO guidelines. The Expert Committee noted that the available evidence for the use of dolutegravir in children was largely limited to pharmacokinetic and safety data from two ongoing paediatric trials, but considered that extrapolation of efficacy from adult trials was acceptable (2).

Public health relevance

According to UNAIDS global aids update of 2020, there were 38 million people living with HIV/AIDS globally, 1.7 million new HIV-1 infections (a decrease of 23% since 2010) and 690 000 thousand HIV-related deaths. Over 95% of people infected with HIV live in low- and middle-income countries 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 other countries 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, about 25.4 million people were receiving antiretroviral therapy in 2019, an estimated two thirds of the people infected with HIV (3). There were 150 000 new HIV infections in children aged 0 to 14 years in 2019 (3). Evidence shows that in the absence of antiretroviral therapy, more than 50% of HIV-infected infants progress to AIDS or death by the age of 2 years (4). The introduction of effective paediatric antiretroviral therapy has changed HIV infection in children from a life-threatening illness to a chronic-but-manageable infection, albeit highly dependent on good adherence to treatment. Despite recognition of the advantages of early treatment, paediatric treatment coverage still reached only 53% of children eligible for treatment in 2019 (3) and data consistently show children are less likely than adults to achieve viral suppression (5). Antiretroviral therapy based on non-nucleoside reverse-transcriptase inhibitors has been widely used in paediatric patients for both prevention of HIV transmission and treatment. A recent survey of newly diagnosed children in five sub-Saharan African countries found resistance to one or more non-nucleoside reverse-transcriptase inhibitors in up to 53% of these children (6). The increasing prevalence of resistance to the previously recommended first-line antiretrovirals has prompted WHO to recommend rapid transition to dolutegravir-based treatment as formulations suitable for children become available. Although global clinical experience with the use of dolutegravir in younger children is limited, it is recommended in this population based on extrapolation of efficacy from the larger, more diverse adult studies. Thus, the most recent WHO treatment guidelines for paediatric use of dolutegravir are based primarily on aligning pharmacokinetic data collected in clinical trials on children receiving dolutegravir to adult pharmacokinetic targets. As a result, adolescents and older children are increasingly receiving dolutegravir-based therapy using adult formulations found to be highly effective. Approval of dolutegravir 10 mg scored, dispersible tablets will allow the use of optimal regimens in both high- and low-income settings across all paediatric age groups.

Benefits

The paediatric data presented and published to date is from two ongoing clinical trials, IMPAACT P1093 and ODYSSEY. Both trials evaluated dolutegravir in paediatric patients, down to 4 weeks of age and weighing 3 kg, using a combination of dispersible tablets and film-coated tablets depending on the study participants' age, weight and ability to swallow tablets. No data are currently available to support giving dolutegravir to infants younger than 4 weeks of age (neonates) or to preterm infants. IMPAACT P1093 is an ongoing single-arm, open-label trial of dolutegravir in children with HIV. The United States (US) Food and Drug Administration's (FDA's) initial approval of dolutegravir for use in children weighing at least 40 kg was based on data from 23 adolescents who had received antiretroviral therapy but not integrase inhibitors (12 to < 18 years) (7). These data have been previously described in the application for dolutegravir 50 mg to be added to the EMLc in 2019 (2). Data from the P1093 trial included: cohorts 1 (12 to < 18 years) and 2 (6 to < 12 years), which provided evidence supporting the use of dolutegravir 50 mg film-coated tablets in paediatric patients weighing more than 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 the use of dolutegravir 25 mg 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 dolutegravir film-coated tablets or dispersible tablets. These 75 participants ranged in age from 1 to 214 months, 59% were female and 68% were black or African American. Eighty per cent of participants were treatment-experienced, but all were integrase inhibitor-naïve. Of these 75 patients who received either dolutegravir 50 mg film-coated tablets or dolutegravir 25 mg dispersible tablets according to the approved dosing recommendations for their weight band, 42 received dolutegravir 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 (per cent) increase from baseline to week 48 was 141 cells/mm3 (7%). The effectiveness observed in the trial was comparable to that of treatment-experienced adult patients (8–10). The ODYSSEY trial enrolled both treatment-naive and treatment-experienced paediatric patients in the European Union, 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 < 18 years were enrolled; 282 children started dolutegravir as first-line therapy and 392 started dolutegravir as second-line therapy (11). Nested pharmacokinetic sub-studies within ODYSSEY evaluated simplified paediatric dosing aligned with WHO-recommended weight bands. Pharmacokinetic data are available from a cohort of children weighing > 25 kg who switched to dolutegravir 50 mg film-coated tablets (12). Data from another ODYSSEY cohort reported on children weighing 20–< 25 kg who received either dolutegravir 50 mg film-coated tablets or 30 mg of dolutegravir administered as six 5 mg dispersible tablets. Both of these

doses achieved area under the curve (AUC) and Cmax values that were higher than adult pharmacokinetic reference values, but are still acceptable, and both doses achieved Ctrough values that were similar to adult reference values, as was weight-band dosing for infants and children under 20 kg (13,14). Dolutegravir dosing in the ODYSSEY study for weight bands under 20 kg was slightly different from that in P1093, mainly because P1093 was originally designed to dose by age rather than by weight band. Both studies contributed pharmacokinetic data to the regulatory submissions for the innovator's dispersible tablet (Tivicay PD®, dolutegravir 5 mg tablets for oral suspension, ViiV Healthcare). Combined pharmacokinetic data from P1093 and ODYSSEY across all age and weight cohorts form the basis for the current FDA and WHO treatment recommendations and are summarized in Table 2 of the prescribing information on Tivicay and Tivicay PD (8). In addition, modelling and simulation studies that included uridine diphosphate glucuronosyltransferase 1-1 (UGT1A1) maturation in infants was used to support the dose of dolutegravir down to 4 weeks of age and 3 kg. In adult clinical studies to date, dolutegravir-based regimens were either non-inferior or superior in efficacy to comparator regimens containing other integrase inhibitors, boosted protease inhibitors and non-nucleoside reverse-transcriptase inhibitors regardless of patient population. No comparative paediatric trials are available but both the WHO working groups and multiple regulatory agencies (including the FDA and the European Medicines Agency) endorse the concept of extrapolating efficacy from well designed, adequately powered adult trials on the basis of similar pharmacokinetic profiles and supplementary safety data.

Harms

The harms associated with dolutegravir were reviewed and summarized at the time of the previous EML and EMLc applications and the associated evidence is available in the technical reports of the meetings (1,2). The FDA clinical review of the data submitted to support registration of dolutegravir dispersible tablets describes the safety data available from P1093 up to 48 weeks of dosing. In P1093, 13 participants (17%) experienced adverse reactions attributed to dolutegravir and all were assessed as Grade 1 or Grade 2 (mild or moderate). Adverse drug reactions reported in more than one study participant were: decreased blood bicarbonate (three participants), decreased haemoglobin (two participants), decreased neutrophil count (four participants), and immune reconstitution inflammatory syndrome (two participants). In data evaluated by the FDA in support of the dispersible tablet registration, new adverse events occurred in seven participants (7%) in the ODYSSEY safety population (n = 97) through week 24. The only adverse event reported in more than one participant was anaemia in three participants (3%). The following adverse events occurred in only one participant each: neutropenia, diarrhoea, hepatitis A, lower respiratory tract infection, measles, cryptococcal meningitis, otitis media, pneumonia, dehydration and malnutrition. None of these adverse events were thought to be related to the study medicine by the investigators (15). Overall, the safety profile in P1093 participants was comparable to that observed in adults and both formulations were well tolerated by paediatric patients (8–10). Long-term safety assessments in the ODYSSEY trial are ongoing and final data up to 96 weeks of dosing are expected later in 2021.

Cost / cost effectiveness

No known cost–effectiveness studies have been conducted for dolutegravir dispersible scored tablets.

WHO guidelines

WHO's 2018 updated recommendations on first-line and second-line antiretroviral regimens for treatment of HIV in infants and children include dolutegravir as a preferred drug for first-line therapy in all ages for which dosing recommendations and a formulation are available (16). This recommendation predated the availability of a child-friendly dolutegravir formulation but can now be widely applied across ages and weight bands. Dolutegravir should be given together with two nucleoside reverse-transcriptase inhibitors appropriate for paediatric patients (abacavir plus lamivudine, or zidovudine plus lamivudine). In addition, the 2018 WHO guidelines also recommend dolutegravir in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone as the preferred second-line regimen for children with approved dolutegravir dosing for whom non-dolutegravir-based regimens are failing. Dosing recommendations for dolutegravir 10 mg scored dispersible tablets for infants and children 4 weeks and older and weighing ≥ 3 kg are: • 3 kg to < 6 kg, 5 mg once daily (half a tablet) • 6 kg to < 10 kg, 15 mg once daily (1.5 tablets) • 10 kg to < 14 kg, 20 mg once daily (2 tablets) • 14 kg to < 20 kg, 25 mg once daily (2.5 tablets) • ≥ 20 kg, 30 mg once daily (3 tablets). Alternatively, paediatric patients weighing ≥ 20 kg may follow the dosing recommendations using dolutegravir 50 mg tablets (50 mg once daily). Because the dispersible tablets are more bioavailable than the previously approved film-coated tablets, 30 mg given as 3 × 10 mg dispersible tablets provides similar drug exposure as one 50 mg film-coated tablet given once daily (adult dose). HIV infection can be diagnosed with relatively simple, point-of-care, rapid testing kits or in clinic or hospital laboratories. WHO recommends treatment for all patients diagnosed with HIV infection regardless of age, clinical stage or laboratory parameters. While receiving dolutegravir as part of an antiretroviral therapy 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 dolutegravir-based therapy. HIV requires life-long treatment.

Availability

At the time of the recent paediatric dispersible tablet review, the FDA revised dosing recommendations for the 50 mg tablets to allow use in children down to 20 kg. Dolutegravir 5 mg tablets for oral suspension (Tivicay PD, ViiV Healthcare) are approved for infants and children 4 weeks of age and older and weighing 3 kg or more in the United States and the European Union. Registration of tablets for oral suspension (also called dispersible tablets) produced by ViiV Healthcare is in progress in additional countries. Licence agreements for dolutegravir have been made available by innovator companies through the Medicines Patent Pool. In addition, ViiV Healthcare, Clinton Health Access Initiative, Inc. (CHAI), Mylan (now Viatris, Inc.) and Macleods Pharmaceuticals Ltd have formed a novel partnership to accelerate development of an optimized paediatric formulation of dolutegravir and bring it to market in low- and middle-income countries (17). 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 dolutegravir 10 mg scored dispersible tablet (18). This formulation was added subsequently to the WHO prequalification expression of interest list. The FDA granted tentative approval of the first generic version of dolutegravir 10 mg scored dispersible tablets (Mylan, Hyderabad) 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. Another supplier's product (Macleods Pharmaceuticals, Mumbai) is currently under review by both the FDA and the WHO prequalification team.

Other considerations

The FDA approved label for Tivicay branded dolutegravir 50 mg tablets and 5 mg dispersible tablets states that the two dosage forms are not bioequivalent. The relative bioavailability of Tivicay PD is about 1.6-fold higher than Tivicay; therefore, the two dosage forms are not interchangeable on a milligram-to-milligram basis.

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