Dolutegravir + lamivudine + tenofovir

Section: 6. Anti-infective medicines > 6.4. Antiviral medicines > 6.4.2. Antiretrovirals > 6.4.2.5. Fixed-dose combinations of antiretrovirals

ATC codes: J05AR27

Indication	Human immunodeficiency virus disease without mention of tuberculosis or malaria, clinical stage unspecified ICD11 code: 1C62.Z
INN	Dolutegravir + lamivudine + tenofovir
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid:** 50 mg + 300 mg + 300 mg (tenofovir disoproxil fumarate equivalent to 245 mg tenofovir disoproxil)
EML status history	First added in 2019 (TRS 1021)
Sex	All
Age	Adolescents and adults
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 + lamivudine + tenofovir
DrugBank	Dolutegravir, Lamivudine, Tenofovir (Tenofovir disoproxil)

Expert Committee recommendation

The Expert Committee recommended the addition of the fixed-dose combination formulation of dolutegravir + lamivudine + tenofovir disoproxil fumarate to the core list of the EML for treatment of HIV infection in adults and adolescents. The Committee noted the demonstrated efficacy and safety of DTG-based regimens in treatment-naive patients, and that DTG-based regimens are now recommended as preferred first-line therapy in WHO Guidelines for adults and adolescents initiating antiretroviral treatment. The Committee also considered that the availability of fixed-dose combinations of antiretroviral therapies provides benefits to patients in terms of ease of administration and reduced pill burden, which can contribute to improved therapeutic adherence.

Background

The application requested the addition of a fixed-dose combination formulation of dolutegravir, lamivudine and tenofovir disoproxil fumarate (TLD) to the core list of the EML for treatment of HIV infection in adults and adolescents. This fixed-dose combination (FDC) had been previously considered by the Expert Committee for addition to the EML. The component medicines are all included individually on the EML.

Public health relevance

In 2017, UNAIDS reported there were 36.9 million people living with HIV/ AIDS globally, 1.8 million new HIV-1

infections, and 940 000 thousand HIV- related deaths (1). Over 95% of infected people live in low- and middleincome countries (LMICs) 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 others have experienced worrying increases in new HIV infections. Overall, approximately 21.7 million people were receiving antiretroviral therapy (ART) in 2017, but this is estimated to represent only 59% of people living with HIV. Early and effective ART not only significantly improves the health of those people living with HIV, but also reduces transmission of the disease as shown in the recently reported START study (2). For this reason, WHO released guidelines in 2015 calling for treatment for all people with HIV. Easy to administer, highly effective, safe treatment options remain desperately needed in many areas of the world to meet the UNAIDS '90-90-90' targets, which call for 90% of people living with HIV to know their status, 90% of those with known infection to be on ART, and 90% of those on ART to be virally suppressed (i.e. on successful therapy) by the year 2020 (3).

Benefits

The efficacy of dolutegravir (DTG) has been demonstrated in ART-naive subjects in three randomized, controlled, multinational, Phase III studies: SPRING-2 (4), SINGLE (5) and FLAMINGO (6). The findings of these studies were evaluated in the 2017 consideration of dolutegravir by the Expert Committee and are not reproduced here. The safety, tolerability and efficacy of a dolutegravir-based regimen was evaluated in a prospectively-enrolled, open-label cohort of 564 Indian adults receiving dolutegravir in combination with other ARVs (primarily tenofovir disoproxil fumarate (TDF) and lamivudine (3TC) or emtricitabine (FTC)) as either first- or second-line therapy. Among the treatment naive patients initiating DTG plus TDF/3TC or TDF/FTC, all had viral suppression at the 6 month follow-up, and overall, viral suppression occurred in 82.9% at six months (7). The NAMSAL ANRS study randomized HIV-infected adults in Cameroon to receive either a dolutegravir-based regimen (TLD) (n=310) or an efavirenz-containing regimen (TLE-400) (n=303) for first-line treatment. Preliminary efficacy results at 48 weeks on treatment indicate the proportion of patients with HIV RNA <50 copies/mL was 74.5% in the TLD arm and 69% in the TLE-400 arm. Fewer patients with initial HIV RNA levels >100 000 copies/mL had virologic suppression to <50 copies/mL: 66.2% in the TLD arm and 61.5% in the TLE-400 arm. In this study, viral suppression with TLD was numerically higher but not statistically superior to TLE-400; NNRTI resistance was an important determinant of TLE-400 failure (8). In the 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 NNRTIs regardless of patient population. In patients initiating first-line treatment, successful virologic suppression occurred in more patients receiving dolutegravir than the comparators. A systematic review and meta-analysis conducted by WHO in 2016 concluded that among treatment-naive patients, treatment with an integrase inhibitor (particularly DTG) plus two NRTIs, had superior efficacy and tolerance to the current standard of care regimens of efavirenz plus two NRTIs (9).

Harms

The overall safety profile of dolutegravir in adults compared favourably to other ARVs included in the clinical trials reported previously. There have been multiple reports of neuropsychiatric events among patients receiving dolutegravir-based treatment since its approval. Although dolutegravir appears to result in fewer of these events compared to efavirenz in comparative clinical trials (5), some patients receiving dolutegravir experience episodes of insomnia or depression. Causality for these events has been difficult to determine as many patients are reported to have a previous history of psychiatric symptoms. In the South Indian cohort of first- and second-line patients, dolutegravirbased regimens were well tolerated. Mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) decreased slightly in the cohort during the 6-month evaluation period, mean haemoglobin increased slightly, and kidney function remained stable. In this cohort, sleep disturbances and neuropsychiatric symptoms were not reported. The frequency of opportunistic infections decreased from 7.4% prior to starting DTG to 3.3% after six months follow up. None of the patients in this cohort discontinued DTG during the evaluation period. Four deaths were reported (two sepsis and two cytomegalovirus (CMV) encephalitis, considered unrelated to ARVs) (7). A nationwide birth outcomes surveillance programme conducted in Botswana began collecting data

in women initiating dolutegravir in 2014. An initial report of pregnant women who began taking either a dolutegravir- (n=1729) or efavirenz-based (n=4593) treatment regimen identified no difference in risk for adverse birth outcomes, even among those beginning treatment during the first trimester (i.e. post-conception ART) (10). However, an interim analysis of a second surveillance study of women becoming pregnant while already receiving ART (i.e. pre-conception ART) identified an excess number of neural tube defects among infants of women receiving a dolutegravir-based regimen. Neural tube defects were observed in 4 of 426 (0.94%) infants born to women receiving dolutegravir compared to 14 of 11 300 (0.12%) infants born to women receiving any other ART regimen and 61 of 66 057 (0.09%) infants born to HIV-uninfected women. Although none of the affected women were receiving folate supplements, no other risk factors for neural tube defects have been identified (11). This study is ongoing and expects to have a final analysis in 2019. While awaiting the final study results and data from other sources, WHO recommends counselling for women of childbearing potential and access to effective contraception in those receiving dolutegravir. However, they also suggest that an efavirenz-based regimen remains safe and effective in women who plan to become pregnant (12). The NRTI backbone of TDF/3TC has an extensive history of use in ART globally and has accumulated a favourable safety and tolerability profile. Initial concerns regarding potentially serious renal and bone toxicity due to the TDF component have not been borne out over years of clinical experience although it requires dose adjustment in patients with significant renal impairment and so is not generally used in this sub-group. In addition, the potential risks and benefits of wide implementation of TLD were evaluated in a 2018 modelling exercise conducted by a group of independent researchers. The group used existing data to estimate HIV transmission and disease progression (taking into account drug resistance, drug potency, differential viral suppression and clinical outcomes) to compare outcomes of different ART regimens in various scenarios. In their model, the greatest number of disability-adjusted life-years was averted in the scenario providing TLD to all adult patients without restrictions over 20 years compared to adults based on intent to have children and/or dependent on documentation of viral suppression (13).

Cost / cost effectiveness

Various sources indicate an average price per patient per year for the FDC of US$ 74.00. This price is comparable to other first-line regimens. A pricing agreement was announced in July 2017 by the governments of South Africa and Kenya, together with UNAIDS, CHAI, the Bill & Melinda Gates Foundation, Unitaid, the UK Department for International Development, PEPFAR, USAID, and the Global Fund, with Aurobindo and Mylan. Under the agreement, Aurobindo and Mylan agreed to offer TLD at approximately US$ 75 PPPY. This lower price is accessible to public sector purchasers in over 92 LMICs worldwide.

WHO guidelines

The 2016 WHO Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection recommended TDF plus 3TC as a preferred nucleoside/tide backbone in first-line therapy and dolutegravir 50 mg in combination with TDF and 3TC as an alternative first-line regimen (14). In addition, these guidelines reiterate the WHO conclusion that FDCs and oncedaily regimens are most preferred. At that time, TLD was not available as an FDC. In the most recent WHO treatment guidelines update (July 2018), a DTGbased regimen is recommended as a preferred first-line regimen for adults and adolescents living with HIV who are initiating antiretroviral therapy (12).

Availability

This product is currently available for procurement from multiple suppliers (including WHO prequalified manufacturers).

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