

## [Emtricitabine + tenofovir alafenamide](#)

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.

The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Rejected

Section:

[6. Anti-infective medicines](#) [6.4. Antiviral medicines](#) [6.4.2. Antiretrovirals](#) [6.4.2.5. Fixed-dose combinations of antiretrovirals](#)

ATC codes: [J05AR17](#)

Indication

Human immunodeficiency virus disease without mention of associated disease or condition, clinical stage unspecified

ICD11 code: [1C62.Z](#)

INN

Emtricitabine + tenofovir alafenamide

Medicine type

Chemical agent

List type

Core

Formulations

**Oral > Solid:** 200 mg + 10 mg ; 200 mg + 25 mg

EML status history

Application rejected in 2017 ([TRS 1006](#))

Sex

All

Age

Adolescents and adults

Therapeutic alternatives

The recommendation is for this specific medicine

Patent information

Read more [about patents](#).

Wikipedia

[Emtricitabine + tenofovir alafenamide](#)

DrugBank

[Emtricitabine](#),

[Tenofovir alafenamide](#)

Expert Committee recommendation

The Expert Committee did not recommend the addition of the fixed-dose combination formulation of emtricitabine and tenofovir alafenamide to the core list of the EML for treatment of HIV infection in adults and children aged 12 years and older. The Committee noted the suggestion of a better safety profile associated with the TAF combination compared with the corresponding TDF combination but considered this to be of uncertain patient-relevant benefit in the long term (as the benefits were based on surrogate outcome measures). The Committee also noted concerns regarding potential drug-drug interactions of this combination with other medicines, particularly rifampicin. The Committee noted that the TAF combination is not recommended as first-line ART in current WHO guidelines.

Background

The application requested addition of a fixed-dose combination formulation of emtricitabine (FTC) and tenofovir alafenamide (TAF) to the core list of the EML for treatment of HIV infection in adults and children aged 12 years and above, in combination with other antiretroviral agents. This was the first application seeking listing of FTC + TAF for treatment of HIV infection. Neither component medicine is available individually on the EML. A fixed-dose combination (FDC) of FTC with tenofovir disoproxil fumarate (TDF) has been included on the EML since 2007.

Public health relevance

In 2015, there were 36.7 million people living with HIV/AIDS globally, of whom more than 95% were in low- and middle-income countries. There were 2.1 million new HIV-1 infections and 1.1 million HIV-related deaths. Less than half of all infected people were receiving ART in 2015 (1).

Benefits

For FTC + TAF, results from studies involving cobicistat (COBI) + elvitegravir (EVG) + FTC + TAF were presented (2-4). The findings of these studies are available in the summary for the COBI + EVG + FTC + TAF application.

Bioequivalence has been demonstrated between FTC + TAF 200 mg + 10 mg, administered with COBI + EVG, and FTC + TAF 200 mg + 25 mg administered without a pharmacokinetic enhancer and a single-tablet regimen of COBI + EVG + FTC + TAF (5). Results of switching studies presented in the application suggest the efficacy in terms of maintenance of virological suppression of switching to TAF-containing regimens from TDF-containing regimens (4, 6-8), including in patients with renal impairment and multidrug-resistant HIV infection.

Harms

Evidence for harms was taken from the comparison of TAF and TDF in combination with cobicistat, elvitegravir and emtricitabine. Renal effects: Compared with the TDF combination, the TAF combination was found to be associated with smaller mean serum creatinine increases (0.08 versus 0.12 mg/dL;  $P < 0.0001$ ), and less proteinuria (median % change -3 versus 20;  $P < 0.001$ ) at 48 weeks (2). The positive effects of the TAF combination on renal function were maintained at 96 weeks (9). Improvements in renal tubular biomarkers were greater in adolescents given the TAF combination than in those given the TDF combination (3, 10), and in patients switching from a TDF-containing regimen (4, 6, 8). Bone effects: Compared with the TDF combination, the TAF combination was associated with a smaller decrease in bone mineral density (BMD) at lumbar spine (mean % change -1.30 versus -2.86;  $P < 0.0001$ ) and hip

(mean % change -0.66 versus -2.95;  $P < 0.0001$ ) at 48 weeks (2). The effect with the TAF combination on lumbar spine BMD was greater after 96 weeks of treatment (mean % change -0.96% versus -2.79;  $P < 0.001$ ) (9). In adolescent patients, median % change in spine BMD increased in patients in the TAF arm, while it decreased in patients in the TDF arm (1.25% versus -0.99%;  $P < 0.009$ ) (3, 10). Patients switched from TDF-containing regimens to TAF-containing regimens also showed improvements in spine and hip BMD (4, 6). The Expert Committee considered that the measured benefits of the TAF-combination in terms of renal function and bone effects are based on surrogate measures and, with the relatively short-term follow-up (48 weeks), that these may not translate in the longer term into benefits of the same magnitude in more patient-relevant clinical outcomes such as reduced risk of renal failure or fractures.

Cost / cost effectiveness



In USA, wholesale acquisition cost of the FTC + TAF combination described in the application is US\$ 1466 for 30 days' supply (30 tablets). The application states that developing countries classified as low- or lower-middle-income by the World Bank, and countries with unmet HIV/AIDS disease burden, are designated as "access countries" and are charged only for production and related costs. The application also states that the cost of a 30-day supply of FTC + TAF to access countries is US\$ 17 (US\$ 204 per year). By way of comparison, the WHO Global Price Reporting Mechanism reports that the median treatment cost per year in 2016 for FTC + TDF is US\$ 55.10.

WHO guidelines



WHO's 2016 Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (11) make the following recommendations for first-line ART in adults: ■ First-line ART for adults should consist of two nucleoside reverse transcriptase inhibitors plus an NNRTI or an INSTI. ■ TDF + lamivudine (3TC) (or emtricitabine (FTC)) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART (strong recommendation, moderate-quality evidence). ■ If TDF + 3TC (or FTC) + EFV is contraindicated or unavailable, one of the following alternative options is recommended: - AZT + 3TC + EFV - AZT + 3TC + NVP - TDF + 3TC (or FTC) + NVP (conditional recommendation, moderate-quality evidence). - TDF + 3TC (or FTC) + dolutegravir or TDF + 3TC (or FTC) + EFV 400 mg/day may be used as alternatives to initiate ART (conditional recommendation, moderate-quality evidence). Countries should discontinue stavudine use in first-line regimens because of its wellrecognized metabolic toxicities (strong recommendation, moderate-quality evidence).

Availability



This product is currently licensed in Canada, Europe and USA. Gilead has licensing agreements with generic drug manufacturers in China, India and South Africa, as well as the Medicines Patent Pool, allowing production and sale of generic versions of Gilead medicines in 112 developing countries.

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1. AIDS by the numbers - AIDS is not over, but it can be. Geneva: Joint United Nations Programme on HIV/ AIDS; 2016 (<http://www.unaids.org/en/resources/documents/2016/AIDS-by-the-numbers>, accessed 7 February 2017). 2. Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet*. 2015;385(9987):2606-15. 3. Kizito H, Gaur A, Prasitsuebsai W, Rakhmanina N, Lawson E, Yongwu Shao Y et al. Week-24 data from a phase 3 clinical trial of E/C/F/TAF in HIV-infected adolescents [Poster abstract]. In: Conference on Retroviruses and Opportunistic Infections, February 23-26, 2015, Seattle, Washington. San Francisco: International Antiviral Society-USA; 2015 (<http://www.croiconference.org/sites/default/files/uploads/croi2015-program-abstracts.pdf>, accessed 7 February 2017). 4. Pozniak A, Arribas JR, Gathe J, Gupta SK, Post FA, Bloch M et al. Switching to tenofovir alafenamide, coformulated with elvitegravir, cobicistat, and emtricitabine, in HIV-infected patients with renal impairment: 48-week results from a single-arm, multicenter, open-label phase 3 study. *J Acquir Immune Defic Syndr*. 2016;71(5):530-7. 5. Zack J, Chu H, Chuck S, Rhee M, Koziara J, West S et al. Bioequivalence of two co-formulations of emtricitabine/tenofovir alafenamide fixed-dose combinations with 200/10 mg and 200/25 mg. *J Bioequiv Availab*. 2016;8(2):068-73. 6. Mills A, Arribas JR, Andrade-Villanueva J, DiPerri G, Van Lunzen J, Koenig E et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. *Lancet Infect Dis*. 2016;16(1):43-52. 7. Gallant JE, Daar ES, Raffi F, Brinson C, Ruane P, DeJesus E et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. *Lancet HIV*. 2016;3(4):e158-65. 8. Huhn GD, Tebas P, Gallant J, Wilkin T, Cheng A, Yan M et al. A randomized, open-label trial to evaluate switching to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide plus darunavir in treatment-experienced HIV-1-infected adults. *J Acquir Immune Defic Syndr*. 2017;74(2):193-200. 9. Wohl D, Oka S, Clumeck N, Clarke A, Brinson C, Stephens J et al. Brief report: a randomized, double-blind comparison of tenofovir alafenamide versus tenofovir disoproxil fumarate, each coformulated with elvitegravir, cobicistat, and emtricitabine for initial HIV-1 treatment: week 96 results. *J Acquir Immune Defic Syndr*. 2016;72(1):58-64. 10. Gaur AH, Kizito H, Prasitsuebsai W, Rakhmanina N, Rassool M, Chakraborty R et al. Safety, efficacy, and pharmacokinetics of a single-tablet regimen containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in treatment-naive, HIV-infected adolescents: a single-arm, open-label trial. *Lancet HIV*. 2016;3(12):e561-8. 11. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach, second edition. Geneva: World Health Organization; 2016 (<http://www.who.int/hiv/pub/arv/arv-2016/en/>, accessed 7 February 2017).