Emtricitabine + rilpivirine + tenofovir alafenamide

REJECTED

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.

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

ATC codes: J05AR19

Indication	Human immunodeficiency virus disease without mention of tuberculosis or malaria, clinical stage unspecified ICD11 code: 1C62.Z
INN	Emtricitabine + rilpivirine + tenofovir alafenamide
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid:** 200 mg + 25 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 + rilpivirine + tenofovir alafenamide
DrugBank	Emtricitabine, Rilpivirine, Tenofovir alafenamide

Expert Committee recommendation

The Expert Committee did not recommend the addition of a fixed-dose combination formulation of emtricitabine, rilpivirine and tenofovir alafenamide to the core list of the EML for the treatment of HIV infection in patients aged 12 years and above who are antiretroviral treatment-naive and have HIV1-RNA <100 000 copies/mL. The Committee noted that the FDC is not recommended as first-line ART in WHO guidelines and recalled that a similar TDF-based formulation had not been recommended in 2015 for inclusion on the EML on the basis of no clinical advantage over currently recommended formulations being demonstrated. The Committee also noted concerns regarding potential drug–drug interactions of this combination with other medicines, particularly rifampicin.

Background

The application requested addition of a fixed-dose combination formulation of emtricitabine (FTC), rilpivirine (RPV) and tenofovir alafenamide (TAF) to the core list of the EML for the treatment of HIV infection in patients aged 12 years and above who are antiretroviral treatment (ART)-naive and have HIV1-RNA <100 000 copies/mL, and as replacement ART in patients with viral suppression (HIV1-RNA <50 copies/mL) on a stable ART regimen. This was the first application seeking listing of FTC + RPV + TAF for treatment of HIV infection. The component medicines are not currently available individually on the EML. In 2015, the Expert Committee considered an application

seeking listing of a similar FDC formulation, incorporating tenofovir disoproxil fumarate (TDF). The application presented the results of the ECHO and THRIVE studies (1), which effectively compared RPV 25 mg and efavirenz 600 mg. Both treatment groups received a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone. The Expert Committee acknowledged that the data presented in the application supported the efficacy of this FDC but noted that RPV is indicated only for patients with a low viral load (<100 000 copies/mL). The Committee considered that triaging patients according to baseline viral load, or switching regimens after achievement of viral suppression was not consistent with a public health approach and may not be feasible in resource-limited settings. In addition, the Committee noted that RPV would not be suitable for patients coinfected with tuberculosis and taking rifampicin. The Committee noted that the proposed formulation included medicines that were not currently recommended in the WHO guidelines as first-line HIV treatment options and that there was insufficient evidence of a relevant clinical advantage over currently recommended first-line treatments already on the EML. Listing was not recommended (2).

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 (3).

Benefits

The application presented evidence for the effectiveness of FTC + RPV + TAF using data from studies of the individual components. For rilpivirine: Non-inferior efficacy of the regimen containing RPV 25 mg compared with that containing efavirenz (EFV) 600 mg was supported by the pooled results of the ECHO and THRIVE trials for virological outcomes at week 96 in patients with baseline viral load <100 000 copies/mL (83.7% vs 80.8% for RPV and EFV, respectively) (1). A study of a small number (n = 36) of adolescent patients, the PAINT trial, showed pharmacokinetic exposure, treatment response and tolerability of RPV to be comparable to that observed in adults (4). The SPIRIT study investigated non-inferiority of switching virologically supressed patients from a ritonavir-boosted protease inhibitor and a double-NRTI backbone to RPV and FTC + TDF as a simplified treatment regimen (5). At week 24, switching resulted in no significant difference in maintenance of virological suppression and met the criteria for non-inferiority. For FTC + TAF, results from studies involving cobicistat (COBI) + elvitegravir (EVG) + FTC + TAF were presented (6–8). The findings of these studies are available in the summary for the COBI + EVG + FTC + TAF application. Bioequivalence between the proposed FDC and the FTC + TAF component of COBI + EVG + FTC + TAF and RPV was demonstrated in a small phase 1 study of 96 healthy subjects (9). The application also included results from two ongoing switching studies, where week 48 data suggested efficacy in terms of virological suppression being maintained with switching to FTC + RPV + TAF from regimens containing FTC + TDF. To date, these results have been reported only as a conference presentation (10).

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 (6). The positive effects of the TAF combination on renal function were maintained at 96 weeks (11). Improvements in renal tubular biomarkers were greater in adolescents given the TAF combination than in those given the TDF combination (7, 12), and in patients switching from a TDF-containing regimen (8, 13, 14). 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 (6). The effect with the TAF combination on lumbar spine BMD was greater after 96 weeks of treatment (mean % change –0.96% versus –2.79; $P< 0.001$) (11). 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%; $P < 0.009$) (7, 12). Patients switched from TDF-containing regimens to TAF-containing regimens also showed improvements in spine

and hip BMD (8, 13). 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. From the ECHO and THRIVE trials, the rilpivirine-treated group had a lower frequency of treatment-related grade 2–4 adverse events (17% vs 33%). The greatest differences between RPV and EFV treatment groups was seen with treatment-related psychiatric adverse events (16% vs 27%) and skin rash (5% vs 16%) (1).

Cost / cost effectiveness

In USA, wholesale acquisition cost of the FTC + RPV + TAF combination described in the application is US$ 2345.87 for 30 days' supply (30 tablets). The application stated 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 production and related costs. The application also stated that the price for a 30-day supply of the TAF-combination (presumably to access countries) is US$ 32 (US$ 384 per year). By way of comparison, the WHO Global Price Reporting Mechanism reports that the median treatment cost per year in 2016 for the current preferred first-line ART (TDF + FTC + EFV) is US$ 77.12.

WHO guidelines

WHO's 2016 Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (15) make the following recommendations for first-line ART in adults: ■ First-line ART for adults should consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an integrase inhibitor (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 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. The Expert Committee noted that relatively few (1500) adults have been treated with FTC + RPV + TAF to date.

Other considerations

Consistent with the findings of the 2015 Expert Committee, it was also the view of the current Expert Committee that assays required to determine baseline viral load and eligibility for treatment with this combination added complexity to treatment implementation from a public health perspective and may not be feasible in resource-limited settings.

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3. 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).
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