Cobicistat + elvitegravir + emtricitabine+ 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.

ATC codes: J05AR18

Indication	Human immunodeficiency virus disease without mention of tuberculosis or malaria, clinical stage unspecified ICD11 code: 1C62.Z
INN	Cobicistat + elvitegravir + emtricitabine + tenofovir alafenamide
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid:** 150 mg + 150 mg + 200 mg + 10 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	Cobicistat + elvitegravir + emtricitabine+ tenofovir alafenamide
DrugBank	Cobicistat, Elvitegravir, Emtricitabine, Tenofovir alafenamide

Expert Committee recommendation

The Expert Committee did not recommend the addition of the fixed-dose combination formulation of cobicistat, elvitegravir, emtricitabine and tenofovir alafenamide to the core list of the EML for treatment of HIV infection in ART-naive adults and children aged 12 years and above. 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 WHO guidelines. The Committee recalled that a similar TDF-based formulation was not recommended for inclusion on the EML in 2015 on the basis that no clinical advantage over currently recommended formulations had been demonstrated.

Background

The application requested addition of a fixed-dose combination formulation of cobicistat (COBI), elvitegravir (EVG), emtricitabine (FTC) and tenofovir alafenamide (TAF) to the core list of the EML for treatment of HIV infection in antiretroviral treatment (ART)-naive adults and children aged 12 years and above. It was also proposed as replacement ART in patients with viral suppression (HIV1-RNA less than 50 copies/mL) on a stable ART regimen. This was the first application seeking listing of COBI + EVG + FTC + TAF fixed-dose combination (FDC) for treatment of HIV infection. The component medicines are not currently included individually on the EML. In 2015, the Expert Committee considered an application for the listing of a similar FDC formulation, incorporating tenofovir disoproxil fumarate (TDF). The Expert Committee considered that the COBI + EVG + FTC + TDF combination showed non-inferiority in terms of efficacy and safety compared with TDF + FTC (or lamivudine, 3TC) +

efavirenz (EFV), which was the recommended first-line treatment regimen in the 2013 WHO guidelines for treatment of HIV. The Expert Committee acknowledged the advantages offered by an FDC formulation in terms of reducing pill burden and potentially improving adherence, but noted that this FDC had not shown any clinical advantage in terms of efficacy and/ or safety over the currently recommended first-line regimens. The Committee noted that the proposed formulation included medicines that are 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 (1).

Public health relevance

In 2015, there were 36.7 million people living with HIV/AIDS globally, of whom more than 95% were living 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 (2).

Benefits

The application presented a summary of evidence from two randomized, double-blind clinical trials comparing COBI + EVG + FTC + TAF with COBI + EVG + FTC + TDF in 1733 treatment-naive adults with HIV-1 infection. The pooled results of these trials formed the basis for regulatory approval in Europe and USA. The primary efficacy end-point in both studies was the proportion of subjects with viral load <50 copies/mL at week 48. The TAF combination was found to be non-inferior to the TDF combination for the primary outcome (92% versus 90%; adjusted treatment difference 2.0%; 95% confidence interval (CI) –0.7% to 4.7%) (3). At 96 weeks, the proportions with viral load <50 copies/mL were 86.6% and 85.2% in the TAF and TDF arms, respectively (difference 1.5%; 95% CI –1.8% to 4.8%) (4). Evidence was also presented from two studies involving 100 patients, in support of use of the TAF combination in treatment-naive patients aged 12–18 years and weighing at least 35 kg (5, 6). Results were consistent with the findings in adults. The application also presented data from three switching studies in which virologically supressed patients were switched from TDF-based regimens to TAF combination regimens (7–9). Viral suppression at week 48 was observed in 97% and 93% of TAF-based and TDF-based treatment arms, respectively (adjusted difference 4.1%; 95% CI 1.6–6.7) (7). Switching to a TAF-based regimen was not observed to be associated with significant changes in estimated creatinine clearance, while significant improvements were observed in proteinuria, albuminuria and bone mineral density (8). In patients with prior ART failure, a simplified 2-tablet regimen using the TAF FDC plus darunavir was found to be non-inferior to a baseline 5-tablet regimen in terms of durable maintenance of viral suppression (9).

Harms

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 (3). The positive effects of the TAF combination on renal function were maintained at 96 weeks (4). Improvements in renal tubular biomarkers were greater in adolescents given the TAF combination than in those given the TDF combination (5, 6), and in patients switching from a TDF-containing regimen (7–9). 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 (3). The effect with the TAF combination on lumbar spine BMD was greater after 96 weeks of treatment (mean % change –0.96% versus –2.79; $P < 0.001$) (4). 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%; $P < 0.009$) (5, 6). Patients switched from TDF-containing regimens to TAF-containing regimens also showed improvements in spine and hip BMD (7, 8). 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.

Additional evidence

No comparison was made in the application of the TAF-combination versus current recommended first-line ART. Current WHO guidelines recommend TDF + 3TC/FTC + EFV as the preferred first-line therapy (strong recommendation, moderate-quality evidence) (10). The application for inclusion on the EML of COBI + EVG + FTC + TDF in 2015 presented such a comparison, and non-inferiority was demonstrated. The Expert Committee considered that, while it is likely that the TAF combination is non-inferior, no clinical efficacy advantage of COBI + EVG + FTC + TDF over the current recommended first-line regimens was demonstrated.

Cost / cost effectiveness

In USA, wholesale acquisition costs of the TAF combination described in the application was US$ 2577.66 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" which are charged only for production and related costs. It also stated that the price for a 30-day supply of the TAF-combination (to access countries) was US$ 17 (US$ 204 per year). By way of comparison, the WHO Global Price Reporting Mechanism reports the median treatment cost per year in 2016 for the current preferred first-line ART (TDF + FTC + EFV) as US$ 77.12.

WHO guidelines

WHO's 2016 Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (10) 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 + 3TC (or FTC) + EFV as an FDC is recommended as the preferred option to initiate ART (strong recommendation, moderate-quality evidence). ■ If TDF + 3TC (or FTC) + EFV is contraindicated or not available, 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 (DTG) 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 (d4T) use in first-line regimens because of its well-recognized metabolic toxicities (strong recommendation, moderate-quality evidence).

Availability

This product is currently licensed in Australia, 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 HIV medicines in 112 developing countries.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2015 (WHO Technical Report Series, No. 994).
2. JAIDS by the numbers – AIDS is not over, but it can be. Geneva: oint United Nations Programme on HIV/AIDS; 2016 (http://www.unaids.org/en/resources/documents/2016/AIDS-by-the-numbers, accessed 7 February 2017).
3. 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.
4. Wohl D, Oka S, Clumeck N, Clarke A, Brinson C, Stephens J et al. Brief report: a randomized, doubleblind 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.
5. Gaur AH, Kizito H, Prasitsueubsai 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.
6. 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).
7. 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.
8. 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.
9. 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.
10. 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).