Emtricitabine + tenofovir alafenamide

REFUSÉE

Le Comité d'experts, après évaluation, refuse d'inscrire le médicament proposé dans la demande.
La Liste Modèle des Médicaments Essentiels fait état des raisons que les membres du Comité ont identifiées pour refuser l'inscription.

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

Codes ATC: J05AR17

Indication	Human immunodeficiency virus disease without mention of associated disease or condition, clinical stage unspecified Code ICD11: 1C62.Z
INN	Emtricitabine + tenofovir alafenamide
Type de médicament	Chemical agent
Type de liste	Liste de base
Formulations	Oral > Solid: 200 mg + 10 mg ; 200 mg + 25 mg
Historique des statuts LME	Demande refusée en 2017 (TRS 1006)
Sexe	Tous
Âge	Adolescents et adultes
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique
Renseignements sur le brevet	Lire la suite sur les brevets.
Wikipédia	Emtricitabine + tenofovir alafenamide
DrugBank	Emtricitabine, Tenofovir alafenamide

Recommandation du comité d'experts

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.

Contexte

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.

Pertinence pour la santé publique

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).

Bénéfices

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 TDFcontaining regimens (4, 6–8), including in patients with renal impairment and multidrugresistant HIV infection.

Torts

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.

Rapport coût/efficacité

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.

Directives de l'OMS

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).

Disponibilité

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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