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 > 6.4.4. Antihepatitis medicines > 6.4.4.1. Medicines for hepatitis B > 6.4.4.1.1. Medicines for hepatitis B > Nucleoside/Nucleotide reverse transcriptase inhibitors

ATC codes: J05AF13

Indication	Chronic hepatitis B ICD11 code: 1E51.0Z
INN	Tenofovir alafenamide
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid:** 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	Tenofovir alafenamide
DrugBank	Tenofovir alafenamide

Expert Committee recommendation

The Expert Committee did not recommend the addition of tenofovir alafenamide to the core list of the EML for the treatment of chronic hepatitis B infection in adults with compensated liver disease. The Committee noted the suggestion of a better safety profile for TAF compared with TDF in terms of renal and bone toxicity (based on surrogate markers) but considered this to be of uncertain patient-relevant benefit in the long term. The Committee also noted that TAF is not currently included in WHO guidelines.

Background

The application requested addition of tenofovir alafenamide to the core list of the EML for the treatment of chronic hepatitis B infection in adults with compensated liver disease. This was the first application seeking listing of tenofovir alafenamide (TAF) for chronic hepatitis B (CHB). An alternative tenofovir salt, tenofovir disoproxil fumarate (TDF), was added to the EML for this indication in 2015 (1). The recommendation to add TDF was based on evidence from randomized controlled trials supporting the role of TDF in various CHB treatment regimens, significant public health need, and the inclusion of TDF in 2015 WHO CHB treatment guidelines (2).

Public health relevance

Globally, it is estimated that 240 million people are chronically infected with hepatitis B, particularly in low- and

middle-income countries. Prevalence is highest in sub-Saharan Africa and east Asia, where up to 10% of the adult population is affected. Complications of hepatitis B infection, including cirrhosis and hepatocellular carcinoma, are responsible for an estimated 650 000 deaths per year (2).

Benefits

Antiviral activity of TAF over a wide range of doses was found to be comparable to that of TDF 300 mg in patients with CHB. At doses of 25 mg or less, TAF was associated with significantly reduced tenofovir exposure compared with TDF, and the 25-mg dose was selected for development in phase 3 trials (3). The application presented the findings of two phase 3, randomized, double-blind, noninferiority studies comparing TAF 25 mg and TDF 300 mg in 1298 hepatitis B e antigen (HBeAg)-negative and HBeAg-positive patients with CHB (4, 5). The primary end-point in each study was the proportion of patients with hepatitis B virus DNA <29 IU/mL at week 48, with a prespecified non-inferiority margin of 10%. The proportion of patients with alanine aminotransferase (ALT) normalization at week 48 was another measured outcome. There was no significant difference in the proportion of HBeAg-negative patients receiving TAF or TDF who achieved the primary end-point (94% vs 93%, difference 1.8%; 95% confidence interval (CI) –3.6 to 7.2; P = 0.47). In HBeAg-positive patients, the proportions were lower but there was no significant difference (64% vs 67%, difference -3.6%; 95% CI –9.8 to 2.6; P = 0.25). In both studies, patients in the TAF group achieved significantly higher rates of ALT normalization when measured using American Association for the Study of Liver Diseases (AASLD) criteria. Differences were not significant when ALT normalization was measured using less stringent central laboratory criteria. Longer-term follow-up is planned.

Harms

Clinically relevant adverse events involving renal abnormalities and bone toxicity have been associated with TDF (3). Safety outcomes from the two above-mentioned phase 3 studies indicated that most adverse events associated with TAF were of mild to moderate intensity; the commonest were headache, nasopharyngitis and upper respiratory tract infection (4, 5). The incidence of serious adverse events, and discontinuations due to adverse events, was low and similar across treatment groups. Compared with TDF, TAF was associated with smaller increases in serum creatinine from baseline to week 48. The difference was significant only in the study of HBeAG-positive patients. Falls in estimated glomerular filtration rate (eGFR) were significantly smaller in the TAF group compared with the TDF group in both studies, and TAF was also shown to be associated with significantly smaller changes in proteinuria markers for renal tubular function. TAF was associated with significantly smaller reductions in hip and spine bone mineral density compared with TDF (4, 5). TAF was also associated with significantly smaller changes in some biomarkers of bone resorption and formation compared with TDF from baseline to week 48. For further investigation of bone safety with TAF, pooled analyses of the phase 3 studies have been undertaken; to date, findings have been reported only as conference posters and oral presentations but are in line with the results of the primary analyses (6–8).

Additional evidence

Tenofovir alafenamide is a pro-drug of tenofovir, which has been associated with reduced plasma levels of the parent nucleotide at doses considerably lower than the approved dose of TDF. TDF has been associated with renal toxicity linked to active renal secretion via organic anion transporters (OAT) and higher exposure of renal proximal tubules to tenofovir. TAF has not been shown to interact with renal transporters, nor has there been OAT-dependent toxicity, suggesting a potential advantage of TAF over TDF in terms of renal safety (9). WHO’s 2015 Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection identified the need to establish the long-term safety, efficacy and toxicity of TAF versus TDF in patients with CHB infection, with or without HIV coinfection (2).

Cost / cost effectiveness

The cost of TAF described in the application is US$ 10 for 30 days’ supply (US$ 120 per year). This is described as a no-profit price and does not include distribution and other related costs. In comparison, the WHO Global Price

Reporting Mechanism reports the median treatment cost per year for TDF 300 mg as US$ 32.24 in 2016.

WHO guidelines

WHO's 2015 Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection (2) make the following recommendations with regard to the parent nucleotide, tenofovir: ■ In all adults, adolescents and children aged 12 years or more in whom antiviral therapy is indicated, a nucleoside/nucleotide analogue with a high barrier to drug resistance (tenofovir or entecavir) is recommended. Entecavir is recommended in children aged 2–11 years (strong recommendation, moderate-quality evidence). ■ In HBV/HIV coinfected adults, adolescents and children aged 3 years or more, tenofovir + lamivudine (or emtricitabine) + efavirenz as a fixed-dose combination is recommended as the preferred option to initiate antiretroviral therapy (strong recommendation, moderate-quality evidence). ■ In persons with confirmed or suspected antiviral resistance (i.e. history of prior exposure or primary non-response) to lamivudine, entecavir, adefovir or telbivudine, a switch to tenofovir is recommended (strong recommendation, low-quality evidence). Tenofovir dosages recommended in the WHO Guidelines correspond with the available dosages of TDF. WHO Guidelines recognize TAF as an orally bioavailable prodrug of tenofovir that may be associated with less renal and bone toxicity then TDF, and identify the research gap in needing to investigate TAF's long-term safety, efficacy and toxicity.

Availability

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.

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. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf?ua=1, accessed 2 February 2017).
3. Agarwal K, Fung SK, Nguyen TT, Cheng W, Sicard E, Ryder SD et al. Twenty-eight day safety, antiviral activity, and pharmacokinetics of tenofovir alafenamide for treatment of chronic hepatitis B infection. J Hepatol. 2015;62(3):533–40.
4. Buti M, Gane E, Seto WK, Chan HLY, Chuang W-L, Stepanova T et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016;1(3):196–206.
5. Chan HLY, Fung S, Seto WK, Chuang W-L, Chen C-Y, Kim HJ et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016;1(3):185–95.
6. Agarwal K, Furusyo N, Byun KS, Hwang J, Flaherty JF, Kim K et al. Improved renal laboratory parameters in CHB patients treated with TAF compared with tenofovir disoproxil fumarate (TDF). AASLD Abstract 1844. Hepatology. 2016;64(1 (Suppl.)):910A
7. Chuang WL, Seto WK, Inokuma T, Ikeda F, Santantonio TA, Flaherty JF et al. Comparison of markers of bone turnover demonstrates less changes in CHB patients receiving tenofovir alafenamide (TAF) compared with tenofovir disoproxil fumarate (TDF). AASLD Abstract 1856. Hepatology. 2016;61(1 (Suppl.)):916A–7A.
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9. Bam RA, Yant SR, Cihlar T. Tenofovir alafenamide is not a substrate for renal organic anion transporters (OATs) and does not exhibit OAT-dependent cytotoxicity. Antivir Ther. 2014;19(7):687–92.

