Cobicistat + elvitegravir + emtricitabine + tenofovir disoproxil fumarate

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: J05AR09

Indication	Human immunodeficiency virus disease without mention of tuberculosis or malaria, clinical stage unspecified ICD11 code: 1C62.Z
INN	Cobicistat + elvitegravir + emtricitabine + tenofovir
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid:** 150 mg + 150 mg + 200 mg + 300 mg (tenofovir disoproxil fumarate equivalent to 245 mg tenofovir disoproxil)
EML status history	Application rejected in 2015 (TRS 994)
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 disoproxil fumarate
DrugBank	Cobicistat, Elvitegravir, Emtricitabine, Tenofovir disoproxil fumarate (Tenofovir disoproxil)

Summary of evidence and Expert Committee recommendations

Applications were submitted by Gilead Sciences Inc. for inclusion of the fixeddose combination formulations of: ■ cobicistat + elvitegravir + emtricitabine + tenofovir disoproxil fumarate (COBI+EVG+FTC+TDF); and ■ emtricitabine + rilpivirine + tenofovir disoproxil fumarate (FTC+RPV+TDF) on the Model List for treatment of HIV-1 infection in treatment-naive adult patients. In the case of FTC+RPV+TDF, listing was sought for patients with HIV-1 RNA less than or equal to 100 000 copies/mL at the start of therapy and for virologically suppressed patients (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen at the start of therapy. Expert reviews of the application were prepared by two members of the Expert Committee. No public comments on the application were received. WHO's Global update on the health sector response to HIV, 2014 reported that, at the end of 2013, there were approximately 12.9 million people receiving ART globally, 11.7 million of whom were in low- and middle-income countries (1). Recommended ART regimens require the use of three or more drugs in combination, and this represents a large pill burden for patients. Fixed-dose combination formulations are recommended and confer multiple benefits, including a reduced pill burden and better adherence to treatment (2). The 2013 WHO Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection currently recommend that first-line ART in adult patients should consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI). The guidelines recommend use of integrase inhibitors (INI), second-generation NNRTIs and protease inhibitors (PIs) as part of third-line regimens (3). The Committee noted advice from the WHO Department of HIV/AIDS that current recommendations on preferred antiretroviral drugs and regimens would be revised in June 2015 (for publication in November 2015). The Expert Committee noted that other recent international treatment guidelines recommend first-line ART with two

NRTIs and a ritonavir-boosted protease inhibitor (PI/r), an NNRTI or an INI. Specifically, the British HIV Association guidelines, updated in November 2013, recommend that therapy-naive patients start combination ART containing TDF and FTC as the NRTI backbone, and atazanavir (ATV)/r, darunavir (DRV)/r, efavirenz (EFV), raltegravir (RAL) or EVG+COBI as the third agent (4). The guidelines of the European AIDS Clinical Society, updated in November 2014, include co-formulated COBI+EVG+FTC+TDF as a recommended first-line regimen for ART-naive adult HIV-positive persons, but state that it should not be initiated in persons with estimated glomerular filtration rate (eGFR) less than 70 mL/min or, unless it is the preferred treatment, in persons with eGFR less than 90 mL/ min (5). The US Department of Health and Human Services guidelines (last updated May 2014) recommend COBI+EVG+FTC+TDF as first-line therapy only for ART-naive patients with pre-ART creatinine clearance greater than 70 mL/min (6). Emtricitabine and tenofovir are NRTIs, rilpivirine is a second-generation NNRTI, elvitegravir is an integrase inhibitor, and cobicistat is a pharmacokinetic enhancer (of elvitegravir). Cobicistat + elvitegravir + emtricitabine + tenofovir disoproxil fumarate (addition) – EML Two randomized, double-blind, active-controlled phase III trials (Study 102 and Study 103) were presented in the application as evidence for efficacy of COBI+EVG+FTC+TDF in ART-naive patients (7,8). Study 102 compared treatment with COBI+EVG+FTC+TDF with treatment with EFV+FTC+TDF. In Study 103, treatment with COBI+EVG+FTC+TDF was compared with treatment with ATV/r plus FTC+TDF. Both studies assessed non-inferiority of COBI+EVG+FTC+TDF versus the comparator in terms of the proportion of the intention-to-treat population with a viral load less than 50 copies/mL at week 48, with 95% confidence intervals and a prespecified non-inferiority margin of 12%. The Committee noted that the primary efficacy end-point analyses supported the non-inferiority of COBI+EVG+FTC+TDF to the comparator treatment in terms of virological response at week 48 in treatment-naive HIV-1 infected patients in both studies. Virological suppression was maintained through to week 96. The application also presented data from three switching studies in treatment-experienced patients, which demonstrated maintenance of virological suppression following a switch to COBI+EVG+FTC+TDF from ritonavirboosted PI-based regimens (9), NNRTI-based regimens (10) and a regimen of raltegrevir and emtricitabine + tenofovir (11). No evidence was presented in the application to support the efficacy of COBI+EVG+FTC+TDF as second- or later-line ART in patients in whom first- or second-line ART had failed. The Committee noted that the results of an integrated analysis of data from Studies 102 and 103 support COBI+EVG+FTC+TDF as being generally well tolerated with a frequency of treatment-emergent adverse effects similar to the comparator regimens. Emtricitabine + rilpivirine + tenofovir (addition) –EML Two randomized, double-blind, active-controlled phase III trials (ECHO and THRIVE) were presented in the application as evidence for the efficacy of FTC/ RPV/TDF in ARV-naive patients with viral load greater than 5000 copies/mL (12,13). Patients were randomized to 96 weeks' treatment with RPV 25 mg daily or EFV 600 mg daily, plus a fixed-dose background regimen of two NRTIs. The Committee noted that, at 96 weeks, the response rate in pooled analyses of ECHO and THRIVE was 78% in both groups. For patients with HIV-RNA less than or equal to 100 000 copies/mL at baseline, the response rate was 84% with RPV and 80% with EFV (12). Further analysis showed a lower response among RPV-treated patients compared with EFV-treated patients when baseline viral load was greater than 500 000 copies/mL (60% vs 75%; 95% CI: -31.0, 1.8) (14). Safety of FTC/RPV/TDF was assessed in ECHO and THRIVE, and results showed it to be associated with a lower incidence of treatment-related grade 2–4 adverse events compared with EFV + FTC/TDF (14). Overall, the Expert Committee considered that the fixed-dose combination of COBI+EVG+FTC+TDF demonstrated non-inferiority in terms of efficacy and safety compared with TDF+3TC/FTC+EFV, the currently recommended first-line regimen in the WHO guidelines. The Committee acknowledged that a fixed-dose combination formulation offers advantages in terms of reducing pill burden and possibly improving adherence, but noted that no clinical advantage in terms of efficacy and/or safety of COBI+EVG+FTC+TDF over current recommended regimens has been demonstrated. The Committee noted that RPV has been shown to be inferior to EFV in patients with higher viral load and is therefore 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 from one regimen to another following the attainment of virological suppression is not consistent with a public health approach and may not be feasible in resource-limited settings. Moreover, in consideration of patients co-infected with tuberculosis, RPV cannot be co-administered with rifampicin. The Committee noted that both the proposed fixed-dose combination products have wide regulatory approval and marketing authorization in Europe and other high-income countries (including Australia, Japan, the United Kingdom, and USA). The licensing status of these products is under review in numerous low- and middle-income countries. In its application, Gilead advised that it has licensing agreements in place with other manufacturers to produce Gilead HIV medicines at lower cost for low- and middle-income countries. While it acknowledged that the data presented in the applications were supportive of the efficacy of the relevant FDCs being non-inferior to that of the studied comparators, and despite the benefits associated with FDC formulations in treating HIV, the Expert Committee did not recommend the addition of COBI/EVG/FTC/TDF and FTC/RPV/TDF to the Model List of Essential Medicines. The Committee noted that the proposed formulations contain medicines not currently recommended for first-line treatment of HIV infection in WHO guidelines, and considered that there was insufficient evidence of a relevant clinical advantage in terms of efficacy of these FDC combinations over currently recommended first-line treatments that are included on the EML. The Committee noted that the WHO guidelines will be updated later in 2015. References: 1. Global update on the health sector response to HIV, 2014 Geneva: World Health Organization; 2014. Available from:

http://apps.who.int/iris/bitstream/10665/128196/1/WHO_HIV_2014.15_ eng.pdf. 2. Ramjan R, Calmy A, Vitoria M, Mills EJ, Hill A, Cooke G, et al. Systematic review and meta-analysis: patient and programme impact of fixed-dose combination antiretroviral therapy. Trop Med Int Health. 2014;19(5):501-13. 3. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013. Available from: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_ eng.pdf. 4. Williams I, Churchill D, Anderson J, Boffito M, Bower M, Cairns G, et al. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012 (Updated November 2013). HIV Med. 2014;15(Suppl 1):1-85. 5. Guidelines Version 7.1, November 2014 Brussels: European AIDS Clinical Society (EACS); 2014. Available from: http://www.eacsociety.org/files/guidelines_english_71_141204.pdf. 6. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Washington, DC: Department of Health and Human Services; 2015. Available from: http://aidsinfo.nih.gov/contentfiles/ lvguidelines/AdultandAdolescentGL.pdf 7. Clumeck N, Molina JM, Henry K, Gathe J, Rockstroh JK, DeJesus E, et al. A randomized, doubleblind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF vs ritonavir-boosted atazanavir plus emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. J Acquir Immune Defic Syndr. 2014;65(3):e121-4. 8. Wohl DA, Cohen C, Gallant JE, Mills A, Sax PE, Dejesus E, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF versus single-tablet regimen efavirenz/emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. J Acquir Immune Defic Syndr. 2014;65(3):e118-20. 9. Arribas JR, Pialoux G, Gathe J, Di Perri G, Reynes J, Tebas P, et al. Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and tenofovir in adults with virologically suppressed HIV (STRATEGY-PI): 48 week results of a randomised, open-label, phase 3b, non-inferiority trial. Lancet Infect Dis. 2014;14(7):581-9. 10. Pozniak A, Markowitz M, Mills A, Stellbrink HJ, Antela A, Domingo P, et al. Switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of nonnucleoside reverse transcriptase inhibitor with emtricitabine and tenofovir in virologically suppressed adults with HIV (STRATEGY-NNRTI): 48 week results of a randomised, open-label, phase 3b non-inferiority trial. Lancet Infect Dis. 2014;14(7):590-9. 11. Mills A, Crofoot G, Ortiz R, Rashbaum B, Towner W, Ward D, et al. Switching from twice-daily raltegravir plus tenofovir disoproxil fumarate/emtricitabine to once-daily elvitegravir/ cobicistat/emtricitabine/tenofovir disoproxil fumarate in virologically suppressed, HIV-1- infected subjects: 48 weeks data. HIV Clin Trials. 2014;15(2):51-6. 12. Cohen CJ, Andrade-Villanueva J, Clotet B, Fourie J, Johnson MA, Ruxrungtham K, et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. Lancet. 2011;378(9787):229-37. 13. Molina JM, Cahn P, Grinsztejn B, Lazzarin A, Mills A, Saag M, et al. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. Lancet. 2011;378(9787):238-46. 14. Nelson MR, Elion RA, Cohen CJ, Mills A, Hodder SL, Segal-Maurer S, et al. Rilpivirine versus efavirenz in HIV-1-infected subjects receiving emtricitabine/tenofovir DF: pooled 96-week data from ECHO and THRIVE Studies. HIV Clin Trials. 2013;14(3):81-91.