Efavirenz + lamivudine + tenofovir

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

ATC codes: J05AR11

Indication	Human immunodeficiency virus disease without mention of tuberculosis or malaria, clinical stage unspecified ICD11 code: 1C62.Z
INN	Efavirenz + lamivudine + tenofovir
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid:** 400 mg + 300 mg + 300 mg (tenofovir disoproxil fumarate, equivalent to 245 mg tenofovir disoproxil)
EML status history	First added in 2017 (TRS 1006)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Efavirenz + lamivudine + tenofovir
DrugBank	Efavirenz, Lamivudine, Tenofovir disoproxil

Expert Committee recommendation

The Expert Committee recommended a new formulation of efavirenz + lamivudine + tenofovir disoproxil fumarate (TDF) for inclusion in the EML. The Committee noted the favourable benefit–risk profile for the lower-strength efavirenz combination: efavirenz 400-mg combinations were found to be non-inferior to combinations with higher efavirenz doses (600 mg) in terms of efficacy, with reduced toxicity. The Committee also noted that EFV400 + 3TC (or FTC) + TDF is included in the latest WHO HIV treatment guidelines infection as an alternative first-line treatment option for adults and adolescents. As previously, the Committee considered that the availability of FDC ART formulations offer benefits of greater dosing accuracy, ease of administration and reduced pill burden and can contribute to better therapeutic adherence.

Background

The EML currently lists a fixed-dose combination (FDC) formulation of efavirenz (EFV) 600 mg + emtricitabine 200 mg + TDF 300 mg, with annotation that emtricitabine is an acceptable alternative to lamivudine, based on knowledge of pharmacology, resistance patterns and clinical trials of antiretrovirals. The intent of this listing should be interpreted to capture formulations comprising efavirenz 600 mg, lamivudine 300 mg and TDF 300 mg. In effect, the application sought listing of a new strength formulation of efavirenz + lamivudine + TDF.

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 antiretroviral therapy (ART) in 2015 (1).

Benefits

The ENCORE1 study was a randomized, double-blind, placebo-controlled non-inferiority trial that compared antiretroviral regimens containing EFV 400 mg or 600 mg in combination with emtricitabine and TDF at recommended doses (2). At week 96, the proportions of patients with viral load <200 copies/mL were 90.0% and 90.6% in the 400 mg and 600 mg treatment arms, respectively (difference –0.6; 95% confidence interval (CI) –5.2 to 4.0; P = 0.72), supporting non-inferiority. The Expert Committee recalled the accepted therapeutic equivalence between emtricitabine and lamivudine, as noted in current EML listings, and considered that the findings of the ENCORE1 study could be extrapolated to lamivudine-containing regimens.

Harms

Safety outcomes in ENCORE1 showed that the proportions of patients in each group reporting adverse events were similar. For adverse events related to EFV, the proportions of reported adverse events were 39% in the 400-mg group and 48% in the 600-mg group (difference –8.6; 95% CI –16.4 to –0.9; P = 0.03). The proportions of patients reporting serious adverse events were not statistically significantly different between treatment groups (2).

Additional evidence

N/A

Cost / cost effectiveness

The proposed price of EFV400 + 3TC + TDF is US$ 99 per patient per year, which is up to 8% less than the price of EFV600 +3TC + TDF. The price is to be confirmed once the U.S. Food & Drug Administration (FDA) completes the PEPFAR (President’s Emergency Plan for AIDS Relief) review in 2017. The average cost of FDCs is higher than that of their components supplied individually. At health-system level, moderate overall cost-savings are claimed in part because the EFV400 combination has fewer treatment-limiting side-effects.

WHO guidelines

EFV400 + lamivudine (3TC) (or emtricitabine (FTC)) + TDF is included in the 2016 WHO Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection as an alternative first-line treatment option for adults and adolescents (3). EFV600 + 3TC (or FTC) + TDF remains the preferred first-line regimen for adults. A systematic review and network meta-analysis of 71 trials involving 34 032 patients was conducted to inform the WHO guidelines and assessed the comparative evidence of the efficacy and safety of integrase strand transfer inhibitors (INSTI; dolutegravir, raltegravir and elvitegravir + cobicistat) and EFV in adult patients with HIV. The review found moderate-quality evidence of comparable effects in terms of viral load suppression between EFV 400 mg/day and EFV 600 mg/day, and greater effects of EFV 400 mg/day in terms of CD4 cell count recovery. EFV 400 mg/day was protective in terms of treatment discontinuation due to adverse events. There was low-quality evidence of the regimens being comparable with respect to mortality or AIDS-defining illnesses and treatment-emergent serious adverse events. The WHO guidelines note the limited availability of data regarding the safety and efficacy of EFV 400 in pregnant women and patients coinfected with tuberculosis using rifampicin.

Availability

This FDC is produced by Mylan Laboratories Ltd, India. The product was granted tentative approval by the FDA on 10 March 2017 as part of the PEPFAR drug review programme.

1. 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 3 February 2017).
2. Carey D, Puls R, Amin J, Losso M, Phanupak P, Foulkes S et al. Efficacy and safety of efavirenz 400 mg daily versus 600 mg daily: 96-week data from the randomised, double-blind, placebo-controlled, non-inferiority ENCORE1 study. Lancet Infect Dis. 2015;15(7):793–802.
3. 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 3 February 2017).

