HHS Panel on Antiretroviral Guidelines for Adults and Adolescents Recommends a Fixed-Dose Combination Product of Elvitegravir/Cobicistat/Tenofovir/Emtricitabine as an Alternative Regimen in Antiretroviral Treatment-Naive Individuals with HIV-1 Infection

Statement released September 18, 2012

Introduction

Elvitegravir (EVG) is a new HIV-1 integrase strand transfer inhibitor (INSTI). It was recently approved by the U.S. Food and Drug Administration as a part of a co-formulated product in combination with cobicistat (COBI), tenofovir (TDF), and emtricitabine (FTC), as a single-tablet (EVG/COBI/TDF/FTC), once-daily regimen for antiretroviral treatment (ART)-naive HIV-infected patients with estimated creatinine clearance (CrCl) of >70 mL/min.[1]

The Panel recommends:

- **Elvitegravir 150mg/cobicistat 150mg/tenofovir 300mg/emtricitabine 200mg once daily (with food) as an alternative regimen for ART-naive HIV-infected patients with CrCl >70 mL/min (BI).[a]**

See Tables 5a and 5b in the current guidelines for a list of the Panel's preferred and alternative regimens for treatment-naive patients.

Clinical Trial and Safety Data for EVG/COBI/TDF/FTC

In two Phase 3 randomized clinical studies of 1,408 treatment-naive patients (89% male), co-formulated EVG/COBI/TDF/FTC was non-inferior to co-formulated efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC)[2] and ritonavir-boosted atazanavir plus tenofovir/emtricitabine (ATV/r + TDF/FTC),[3] with similar proportion of participants achieving HIV RNA <50 copies/mL at Week 48. Rates of virologic failure were low and comparable across study arms. INSTI-associated mutations were identified in 11 of 26 subjects in the EVG/COBI/TDF/FTC arms who failed therapy and had genotype data available.[2, 3] These mutations conferred varying degrees of cross-resistance to raltegravir and high rates of co-existing nucleoside analog resistance.[1] The most common clinical adverse events reported with EVG/COBI/TDF/FTC were diarrhea, nausea, and headache.

EVG is metabolized through CYP3A enzymes. CYP3A inhibitors or inducers can significantly affect its metabolism. COBI is a potent CYP3A inhibitor with no activity against HIV. It serves as a pharmacokinetic enhancer of EVG, with resultant increase in EVG's systemic exposure and prolongation of its elimination half-life, which allows for once-daily dosing.[4] As a potent CYP3A inhibitor, COBI can inhibit the metabolism of other CYP3A substrates, including other antiretroviral (ARV) drugs such as HIV protease inhibitors, non-nucleoside reverse transcriptase inhibitors, and maraviroc. Currently, co-administration of EVG/COBI/TDF/FTC with other ARV drugs is not recommended. It should be used with caution with many other CYP3A substrates as noted in the product label.[1]

COBI inhibits active tubular secretion of creatinine, resulting in increases in serum creatinine and a reduction in estimated CrCl without reducing glomerular function.[5] In the Phase 3 trials, more subjects discontinued study drugs because of renal adverse events in the EVG/COBI/TDF/FTC arms (eight subjects) than in the comparator arms (one subject in the ATV/r + TDF/FTC arm; none in the EFV/TDF/FTC arm). Four of the eight subjects in the EVG/COBI/TDF/FTC arms who discontinued study drug had evidence of proximal tubular dysfunction. Patients on EVG/COBI/TDF/FTC should be switched to an alternative ART regimen if estimated CrCl decreases to less than 50 mL/min. Concomitant use of nephrotoxic drugs should be avoided.

Summary

EVG/COBI/TDF/FTC is an effective INSTI-based regimen in HIV-infected, ART-naive patients. The co-formulation and long half-life allows for one tablet, once-daily dosing. Limitations include a significant

potential for drug-drug interactions, the availability of only 48 weeks of safety data, usage limited to individuals with pre-treatment CrCl >70 mL/min, a possible increased risk of proximal renal tubulopathy, limited data in patients with advanced HIV disease and in women, and the need for the drug to be taken with food. Based on these factors, the Panel recommends EVG/COBI/FTC/TDF as an alternative regimen for ART-naive patients **(BI)**.

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*[a] **Rating of Recommendations:** A = Strong; B = Moderate; C = Optional*

***Rating of Evidence:** I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion*

References

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