National PBM Drug Monograph

Efavirenz, emtricitabine, and tenofovir (Atripla®)

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

FDA Approved indication: This single tablet regimen is indicated for the treatment of HIV-1 infection in adults as a complete regimen or in combination with other antiretroviral agents.

Dosing: The single fixed dose combination tablet contains efavirenz 600mg, emtricitabine 200mg, and tenofovir 300mg. The dose for individuals with CLcr > 50ml/min is one tablet once a day separated from meals. This single tablet regimen is the first and only product that contains a complete highly active antiretroviral therapy regimen. This triple-drug product should not be used in those with renal insufficiency due to a need to dose reduce the emtricitabine and tenofovir portions (but not efavirenz).

Pharmacology: All three ingredients work by inhibiting reverse transcriptase, an enzyme required for HIV replication, either non-competitively (efavirenz) or competitively (emtricitabine and tenofovir). One Atripla tablet was determined to be bioequivalent to one efavirenz 600mg tablet and one Truvada ® (emtricitabine 200mg + tenofovir 300mg) tablet in a 2-way randomized, single-dose, crossover study in 48 healthy subjects (73% female, 90% Hispanic).[1] Subjects were evaluated in the fasted state. The combination product produces blood levels for each of the active ingredients adequate to achieve efficacy, with a 90% CI for the geometric mean ratio (GMR) of Cmax and AUC for the single tablet regimen contained within 80-125% of the individual agents.

The terminal half-life of each of the components varies as follows: emtricitabine 10 hours, tenofovir 17hours, and efavirenz between 40-55 hours.[2-4] The terminal half-life of efavirenz can be markedly prolonged in those with the 516T/T variant of the CYP 2B6 gene. Because of the differing half-lives of these agents with efavirenz being substantially longer, discontinuation of the fixed dose product may result in functional monotherapy with efavirenz increasing the risk of selection of NNRTI-mutations.[5] In the PK study described above, measurable efavirenz concentrations were detected beyond 21days, compared with 96 and 72 hours for emtricitabine and tenofovir, respectively.[1] The optimal time sequence for staggering the discontinuation of components has not been determined for this or any other NNRTI based regimen. Some experts recommend discontinuing the efavirenz component first and continuing the NRTI backbone either alone or in combination with a protease inhibitor for anywhere from 4 days up to four weeks after discontinuation of the efavirenz.[5]

Drug Interactions: Efavirenz has been shown in vivo to induce CYP3A4 resulting in decreased concentrations of co-administered agents metabolized by this pathway. Drugs which should not be coadministered with efavirenz include: astemizole, midazolam, triazolam, cisapride, ergot derivatives, and voriconazole. Drugs that require dose adjustment include atazanavir, indinavir, lopinavir/ritonavir, methadone, rifabutin, and sertraline. In vitro, efavirenz has been shown to inhibit 2C9, 2C19, and 3A4. Because efavirenz is metabolized by CYP3A4, drugs which induce 3A4 (i.e. phenobarbital, rifampin, and rifabutin) may increase the clearance of efavirenz.[4]

Neither emtricitabine nor tenofovir is an inhibitor or inducer of CYP450 enzymes and there are no reported significant drug-interactions with either agent via this mechanism. Because tenofovir is excreted partially by active tubular secretion, there is the potential for competition of this elimination pathway if administered with other drugs eliminated via active tubular secretion. Co-administration of tenofovir and didanosine significantly increases the concentration of didanosine

by an unknown mechanism and requires a decreased dose of didanosine. Pharmacokinetic studies of tenofovir and atazanavir revealed decreased concentrations of atazanavir even in the presence of ritonavir, though to a lesser degree.[3]

Safety: The fixed dose combination of efavirenz/emtricitabine/tenofovir was reportedly generally well tolerated with most AEs being mild, transient, and consistent with known safety profiles of the individual agents.[1] Two SAEs occurred, both spontaneous abortions in the first trimester. It should be noted that efavirenz is a category D agent and should be avoided in pregnancy. CNS adverse events were the most frequently reported drug-related AEs, primarily dizziness and headache (24% with the single tablet and 29% with individual components). Other possible adverse events and reactions from the co-formulated product of efavirenz, emtricitabine and tenofovir can only be extrapolated from trials where either drug was used alone or in combination with the others. When used as separate agents as part of a combination regimen, side effects occurring in >5% of patients included: dizziness, nausea, diarrhea, fatigue, headache, and rash.[6] Laboratory abnormalities included elevated amylase, triglycerides, and creatinine phosphokinase, hematuria, and elevated liver function tests.[6] Other important side effects reported with efavirenz include serious psychiatric symptoms including severe depression and suicidal ideation. Insomnia, impaired concentration, somnolence, abnormal dreams, and hallucinations have been reported in patients taking efavirenz, however, these symptoms generally resolve after the first 2-4 weeks of therapy.[4] Skin hyperpigmentation, primarily on the palms and soles after 3 months of exposure, has been associated with emtricitabine therapy.[2] Renal impairment, including acute renal failure and Fanconi syndrome, has been reported with tenofovir. Most cases have occurred in patients with underlying systemic or renal disease or in patients receiving other nephrotoxic agents. Significant decreases in bone mineral density at the lumbar spine and hip have also been reported in patients receiving a tenofovir containing regimen.[3] Because emtricitabine and tenofovir have activity against hepatitis B, cases of hepatitis B "flare up" were reported after discontinuing therapy with these agents. Lactic acidosis and severe hepatomegaly with steatosis have been associated with NRTI use.[2,3] Fat redistribution and immune reconstitution syndrome have been reported with the use of NRTIs and NNRTIs, alone or in combination with other antiretrovirals, and are considered class effects.[2-5] As with all HIV related clinical trials, the exact rate of adverse events due to a single drug is difficult to evaluate given the required use of multiple, concurrent drugs, to manage HIV infection.

Laboratory monitoring should include periodic assessment of renal function as emtricitabine and tenofovir require dose adjustment in patients with renal impairment.

Efficacy: Only bioequivalence data was required for submission of the NDA for this fixed dose combination to the FDA., Therefore, no new clinical efficacy trials using this product are available for review. Because each of the products already is separately approved and there are studies showing that the products can be safely and effectively used together, no new preclinical or safety and efficacy data was required for the application. For these types of FDA submissions, the FDA has formally stated that clinical support for a fixed dose combination product should include efficacy and safety data from at least one well-controlled study for at least 48 weeks in duration and be designed to demonstrate statistical noninferiority, or superiority, of the regimen to an accepted control regimen.[7] Such a noninferiority study has been published comparing tenofovir, emtricitabine and efavirenz given once daily as single components to a fixed dose of zidovudine +lamivudine given twice daily plus efavirenz given once daily.[6] This prospective clinical trial in HIV-infected drug naïve subjects was an open-label study involving 517 patients randomly assigned to either drug regimen and who had no evidence of baseline resistance to efavirenz. The primary endpoint was the proportion of patients in whom the HIV RNA level was <400copies/mL at 48 weeks. Of the 244 patients in the tenofovir, emtricitabine and efavirenz group reaching 48 weeks, 84% had an HIV RNA <400copies/mL compared to 73% of the 243 patients in the zidovudine+lamivudine and efavirenz group (p=0.002) which excluded inferiority. Similarly, 77% of patients in the tenofovir, emtricitabine group had HIV RNA levels <50copies/mL

compared to 68% in the zidovudine+lamivudine group (p=0.03). CD4 responses were also greater in this group with a mean increase of 190 vs. 158 cells/mm3 (p=0.002). It is important to note that the difference in the proportion of patients who achieved and maintained HIV RNA < 400 copies/mL largely results from the higher number of discontinuations due to adverse events in the zidovudine+lamivudine group. Although the overall percent of adverse events was the same in each group (63%), significantly more patients in the zidovudine+lamivudine group discontinued treatment do to adverse events (p=0.02). This was primarily due to marked anemia.

Guidelines issued by the US Department of Health and Human Services (DHHS) list the combination of efavirenz, emtricitabine, and tenofovir as a preferred NNRTI-based treatment regimen for use in appropriate patients who are antiretroviral naïve.[5]

This three drug combination is also commonly used in treatment-experienced patients.

Cost: The 30 day equivalent cost of the three drug combination ($713.80) contained in Atripla® is the same whether the regimen is comprised of the new co-formulated product, the combination of efavirenz (Sustiva®) and the dual combination drug emtricitabine/tenofovir (Truvada®), or the three separate ingredients as efavirenz (Sustiva®), emtricitabine (Emtriva®), and tenofovir (Viread®). The cost of distribution (stocking, handling, mailing) may be less for the combination product. In addition, veterans who have a pharmacy copay will pay less for one instead of two or three products.

Conclusion: This combination product, the first of which contains a complete highly active antiretroviral regimen, will simplify dosing of HIV therapy for providers and patients. Atripla® helps to address a continued clinical need for simplified once daily regimens for HIV-1 infected patients. Other benefits include stocking of fewer bottles of the individual components, filling and/or refilling/copays for only 1 medication instead of 2 or 3, improved adherence due to a single pill with once daily frequency, and subsequent decreases in partial treatments. These benefits come at a drug procurement cost neutral price.

Prescribing and dispensing of Atripla® is likely to be prone to medication errors due to confusion between the single-, dual-, and triple- ingredient products.

Because of the differing half-lives of these agents with efavirenz being substantially longer, discontinuation of the fixed dose product may result in functional monotherapy with efavirenz increasing the risk of selective resistance.

Recommendation: Atripla® should be added to the national formulary. Since the components of this triple formulation will be needed in other veterans, these single- and dual-ingredient medications should not be removed from formulary and replaced with Atripla®.

References:

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2. Package Insert. Emtriva (emtricitabine) Capsules. Foster City, CA: Gilead Sciences, September 2005.

3. Package Insert. Viread (tenofovir disoproxil fumarate) Tablets. Foster City, CA: Gilead Sciences, March 2006.

4. Package Insert. Sustiva (efavirenz) capsules and tablets. Princeton, NJ: Bristol-Myers Squibb Company, February 2005.

5. Department of Health and Human Services (DHHS). Panel on Clinical Practice for Treatment of HIV Infection convened by the Department of Health and Human Services: Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. May 4, 2006 (cited: May 12, 2006). Available at: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

6. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. NEJM 2006; 354:251-60.

7. Department of Health and Human Services (DHHS), Food and Drug Administration, and Center for Drug Evaluation and Research (CDER). Guidance for industry fixed dose combination and co-packaged drug products for treatment of HIV. May 2004. (cited: May 12, 2006). Available at: http://www.fda.gov/ohrms/dockets/98fr/04D-0228-GDL0001-6283dft.doc.

8. Package Insert. Atripla® (efavirenz/emtricitabine/tenofovir). Bristol-Myers Squibb & Gilead Sciences, LLC. July 2006

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