Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Elvitegravir (EVG) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Only available in fixed-dose combination tablets (Stribild):

Elvitegravir (EVG) + cobicistat (COBI) + emtricitabine (FTC) + tenofovir disoproxil fumarate (TDF)

EVG 150 mg + COBI 150 mg + FTC 200 mg + TDF 300 mg

Dosing Recommendations

Pediatric dose (aged <18 years):

- Not FDA-approved or -recommended for use in children aged <18 years.

Adult dose (aged ≥18 years):

- 1 tablet once daily in antiretroviral (ARV) treatment-naive adults.

Selected Adverse Events

- Diarrhea, nausea, flatulence
- Renal insufficiency
- Cobicistat alters tubular secretion of creatinine, and therefore, may decrease creatinine-based estimates of glomerular filtration rate without a true change in glomerular filtration.
- Decreased bone mineral density (BMD)

Special Instructions

- Administer with food.
- Monitor estimated creatinine clearance, urine glucose, and urine protein; in patients at risk of renal impairment, also monitor serum phosphate. Patients with increase in serum creatinine >0.4 mg/dL should be closely monitored for renal safety.
- Screen patients for hepatitis B virus (HBV) infection before use of FTC or TDF. Severe acute exacerbation of HBV can occur when FTC or TDF are discontinued; therefore, monitor hepatic function for several months after therapy with FTC or TDF is stopped.
- Not recommended for use with other ARV drugs.

Metabolism

- Stribild should not be initiated in patients with estimated creatinine clearance (CrCl) <70 mL/min and should be discontinued in patients with estimated CrCl <50 mL/min.
- Stribild should not be used in patients with severe hepatic impairment.

Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- *Metabolism:* Stribild contains elvitegravir and cobicistat. Elvitegravir is metabolized by cytochrome P (CYP) 3A4 and is a modest inducer of CYP2C9. Cobicistat is an inhibitor of CYP3A4 and a weak inhibitor of CYP2D6; in addition, it inhibits ATP-dependent transporters BCRP and P-glycoprotein and the organic anion transporting polypeptides OAT1B1 and OAT1B3. Potential exists for multiple drug interactions.
- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir or emtricitabine. Concomitant use of nephrotoxic drugs should be avoided.
- *Protease inhibitors (PIs):* Stribild should not be administered concurrent with products or regimens containing ritonavir because of similar effects of cobicistat and ritonavir on CYP3A.
- Not recommended for use with other ARV drugs.

Major Toxicities:

- *More common:* Nausea, diarrhea, and flatulence.
- *Less common (more severe):* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with nucleoside reverse transcriptase inhibitors including tenofovir disoproxil fumarate (tenofovir) and emtricitabine. Tenofovir caused bone toxicity (osteomalacia and reduced bone density) in animals when given in high doses. Decreases in bone mineral density have been reported in both adults and children taking tenofovir; the clinical significance of these changes is not yet known. Evidence of renal toxicity, including increases in serum creatinine, blood urea nitrogen, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate, has been observed. Numerous case reports of renal tubular dysfunction have been reported in patients receiving tenofovir; patients at increased risk of renal dysfunction should be closely monitored.

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

Pediatric Use: Elvitegravir is only available as the fixed-dose combination product Stribild, which contains elvitegravir/cobicistat/emtricitabine/tenofovir. Stribild is not U.S. Food and Drug Administration (FDA)-approved for use in children aged <18 years. There are no data on its use in individuals aged <18 years.

Elvitegravir is an integrase strand transfer inhibitor that is metabolized rapidly by CYP3A4. Cobicistat itself does not have ARV activity, but is a CYP3A4 inhibitor added as a pharmacokinetic enhancer. Cobicistat slows elvitegravir metabolism and allows once-daily administration of the combination. Stribild is FDA-approved as a complete ARV regimen in HIV-1-infected ARV-naive adults aged ≥18 years[1] based on trials showing non-inferiority to regimens of emtricitabine/tenofovir plus atazanavir/ritonavir,[2] or emtricitabine/tenofovir plus efavirenz.[3] There is cross-resistance between elvitegravir and raltegravir.[4] Cobicistat alters the renal tubular secretion of creatinine, so creatinine-based calculations of estimated glomerular filtration rate will be altered, even though the actual glomerular filtration rate might be only minimally changed.[5] Adults who experience a confirmed increase in serum creatinine greater than 0.4 mg/dL from baseline should be closely monitored for renal toxicity.[1]

References

1. Food and Drug Administration. Stribild Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203100s000lbl.pdf. 2012.
2. DeJesus E, Rockstroh JK, Henry K, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: A randomised, double-blind, phase 3, non-inferiority trial. *Lancet*. Jun 30 2012;379(9835):2429-2438. Available at http://www.ncbi.nlm.nih.gov/pubmed/22748590.
3. Sax PE, DeJesus E, Mills A, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: A randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. *Lancet*. Jun 30 2012;379(9835):2439-2448. Available at http://www.ncbi.nlm.nih.gov/pubmed/22748591.
4. Garrido C, Villacian J, Zahonero N, et al. Broad phenotypic cross-resistance to elvitegravir in HIV-infected patients failing on raltegravir-containing regimens. *Antimicrob Agents Chemother*. Jun 2012;56(6):2873-2878. Available at http://www.ncbi.nlm.nih.gov/pubmed/22450969.
5. German P, Liu HC, Szwarcberg J, et al. Effect of cobicistat on glomerular filtration rate in subjects with normal and impaired renal function. *J Acquir Immune Defic Syndr*. Sep 1 2012;61(1):32-40. Available at http://www.ncbi.nlm.nih.gov/pubmed/22732469.