### Elvitegravir (EVG) (Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information see Drugs@FDA: [http://www.accessdata.fda.gov/scripts/cder/daf](http://www.accessdata.fda.gov/scripts/cder/daf)

#### Formulations

**Tablet:** Discontinued by the manufacturer. Only available in fixed-dose combination tablets.

**Fixed-Dose Combination Tablets:**

- **[Genvoya]** Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus tenofovir alafenamide (TAF) 10 mg
- **[Stribild]** Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus tenofovir disoproxil (TDF) 300 mg

#### Dosing Recommendations

**[Genvoya] Elvitegravir plus Cobicistat plus Emtricitabine plus TAF**

**Pediatric (Weighing <25 kg) Dose:**
- No data on appropriate dose of elvitegravir in Genvoya for children weighing <25 kg

**Child and Adolescent (Weighing ≥25 kg: Any Sexual Maturity Rating [SMR]) and Adult Dose:**
- One tablet once daily

**[Stribild] Elvitegravir plus Cobicistat plus Emtricitabine plus TDF**

**Pediatric (Weighing <35 kg) Dose:**
- No data on appropriate dose of elvitegravir in Stribild for children weighing <35 kg

**Adolescent (Weighing ≥35 kg and SMR 4 or 5) and Adult Dose:**
- One tablet once daily

**Note:** Stribild and Genvoya are Food and Drug Administration approved for use in ARV treatment-naive patients or to replace the current ARV regimen in patients who are virologically suppressed (HIV-1 RNA <50 copies/mL) on at stable ARV regimen for at least 6 months with no history of treatment failure and no know substitutions associated with resistance to the individual components of Genvoya or Stribild.

#### Selected Adverse Events

**Elvitegravir-Associated Adverse Events:**
- Diarrhea

**Stribild-Associated Adverse Events:**
- Nausea
- Diarrhea
- Fatigue
- Headache

**TDF-Specific Adverse Events:**
- Renal insufficiency
- Decreased bone mineral density
- Flatulence

**Cobicistat-Specific Adverse Events:**
- Alteration in tubular secretion of creatinine

**Genvoya-Associated Adverse Events:**
- Nausea
- Diarrhea
- Fatigue
- Headache

**TAF-Associated Adverse Events:**
- Increased low-density lipoprotein-cholesterol and total cholesterol

**Cobicistat-Associated Adverse Events:**
- Alteration in tubular secretion of creatinine

#### Special Instructions

- Administer with food.
- When using Stribild, which contains TDF, monitor estimated creatinine clearance (CrCl),
Drug Interactions (see also the Adult and Adolescent Guidelines and the HIV Drug Interaction Checker)

- **Metabolism**: Stribild and Genvoya contain elvitegravir and cobicistat. Elvitegravir is metabolized predominantly by cytochrome P (CYP) 450 3A4, secondarily by uridine diphosphate glucuronosyltransferase (UGT) 1A1/3, and by oxidative metabolism pathways. Elvitegravir is a modest inducer of CYP2C9. Cobicistat is an inhibitor of CYP3A4 and a weak inhibitor of CYP2D6; in addition, cobicistat inhibits the adenosine triphosphate-dependent transporters BCRP and P-glycoprotein and the organic anion-transporting polypeptides OAT1B1 and OAT1B3. There is potential for multiple drug interactions when using both elvitegravir and cobicistat.

- **Renal elimination**: Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir disoproxil fumarate (TDF) or emtricitabine. Concomitant use of nephrotoxic drugs should be avoided when using Stribild.
• **Absorption:** Elvitegravir plasma concentrations are lower with concurrent administration of antacids because of the formation of complexes in the gastrointestinal tract and not because of changes in gastric pH. Separate administration of Genvoya and antacids by at least 2 (preferably 4) hours. Absorption of integrase inhibitors, including elvitegravir, is decreased by chelation by high concentrations of divalent cations like iron, so administration of Genvoya should be separated from administration of iron supplements or multivitamins containing iron, by at least 4 hours.

• **Protease inhibitors:** Neither Stribild nor Genvoya should be administered concurrently with products or regimens containing ritonavir due to the similar effects of cobicistat and ritonavir on CYP3A4 metabolism.

• Neither Stribild nor Genvoya is recommended for use with other antiretroviral (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 TDF and emtricitabine. TDF caused bone toxicity (osteomalacia and reduced bone mineral density [BMD]) in animals when given in high doses. Decreases in BMD have been reported in both adults and children taking TDF; the clinical significance of these changes is not yet known. Evidence of renal toxicity has been observed in patients taking TDF, including increases in serum creatinine, blood urea nitrogen, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate. Numerous case reports of renal tubular dysfunction have been reported in patients receiving TDF; patients at increased risk of renal dysfunction should be closely monitored if treated with Stribild.

**Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation. There is phenotypic cross-resistance between elvitegravir and raltegravir.¹

**Pediatric Use**

**Approval**

Elvitegravir was Food and Drug Administration (FDA)-approved in 2014 as a tablet (Vitekta) for use in adults in combination with a protease inhibitor plus ritonavir. The drug manufacturer removed Vitekta from the market in February 2017 and elvitegravir is no longer available as a single-agent ARV.

Elvitegravir was FDA-approved in 2012 for use in adults as part of the fixed-dose combination product Stribild, which contains elvitegravir, cobicistat, emtricitabine, and TDF. Stribild is FDA-approved for use in children aged ≥12 years and weighing ≥35 kg.²⁻³

Genvoya, a fixed-dose combination product which contains elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (TAF), was FDA-approved for use in children aged ≥12 years and weighing ≥35 kg in November 2015. In September 2017, Genvoya was FDA-approved for use in children aged >6 years and weighing >25 kg.⁴

**Efficacy in Clinical Trials**

A combination of elvitegravir/cobicistat/emtricitabine/TDF was found to be non-inferior to a regimen of efavirenz/emtricitabine/TDF⁵ and non-inferior to a regimen of atazanavir/ritonavir (ATV/r) with emtricitabine/TDF in adults at 144 weeks of treatment.⁶ In two studies, 1,733 adults were randomly assigned to receive either elvitegravir/cobicistat/emtricitabine/TDF or elvitegravir/cobicistat/emtricitabine/TAF. After 48 weeks, those receiving elvitegravir/cobicistat/emtricitabine/TAF had significantly smaller mean serum creatinine increases (0.08 vs. 0.12 mg/dL; P < 0.0001), significantly less proteinuria (median percent change...
-3% vs. 20%; $P < 0.0001$), and a significantly smaller decrease in BMD at the spine (mean percent change -1.30% vs. -2.86%; $P < 0.0001$) and hip (-0.66% vs. -2.95%; $P < 0.0001$).  

Formulations

Elvitegravir is an integrase strand transfer inhibitor that is metabolized rapidly by CYP3A4. Elvitegravir must be used in the fixed-dose combination products Stribild or Genvoya, which contain cobicistat (see below). Cobicistat itself does not have ARV activity, but is a CYP3A4 inhibitor that acts as a pharmacokinetic (PK) enhancer, similar to ritonavir.

Stribild is FDA-approved as a complete antiretroviral therapy (ART) regimen in ARV-naive adults with HIV-1 aged ≥18 years or to replace the current ART regimen in those who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable ART regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Stribild. Trials have shown that Stribild is non-inferior to regimens of emtricitabine combined with TDF plus ATV/r, or emtricitabine plus TDF plus efavirenz. Cobicistat inhibits renal tubular secretion of creatinine, and serum creatinine will often increase soon after initiation of treatment with Stribild. Therefore, creatinine-based calculations of estimated glomerular filtration rate (GFR) will be altered, even though the actual GFR might be only minimally changed. Adults who experience a confirmed increase in serum creatinine >0.4 mg/dL from baseline should be closely monitored for renal toxicity by following creatinine for further increases and urinalysis for evidence of proteinuria or glycosuria. Careful periodic evaluation of renal function is warranted because Stribild contains TDF, which can be associated with renal toxicity. This nephrotoxicity may be more pronounced in patients with pre-existing renal disease.

Genvoya is FDA-approved as a complete ART regimen in ARV-naive individuals with HIV-1 aged ≥6 years and weighing ≥25 kg or to replace the current ARV regimen in those who are virologically suppressed (i.e., HIV-1 RNA <50 copies/mL) on a stable ART regimen for at least 6 months, with no history of treatment failure and no known substitutions associated with resistance to the individual components of Genvoya. Because Genvoya contains TAF instead of TDF, Genvoya would be expected to have less bone and renal toxicity compared to Stribild. Two studies of adults have shown that Genvoya has diminished renal and bone toxicity when compared to Stribild. After 48 weeks of treatment, participants treated with Genvoya had significantly smaller increases in serum creatinine, less proteinuria, and smaller decreases in BMD at the spine and hip than participants treated with Stribild.

Use of Elvitegravir as Stribild or Genvoya in Adolescents Aged 12 to 18 years

Studies of the adult dosage formulation of Stribild used in children with HIV aged ≥12 years and weighing ≥35 kg have demonstrated PK, safety, and efficacy similar to that in adults through 24 weeks of study. Studies of the adult dosage formulation of Genvoya in children with HIV aged ≥12 years and weighing ≥35 kg have shown safety comparable to that of adults, and this formulation is FDA-approved for use in this age/weight group. Genvoya is preferable to Stribild for treatment of youth with sexual maturity rating 1 to 3 because of the diminished renal and bone toxicity of Genvoya compared with Stribild.

Use of Elvitegravir as Genvoya in Children Aged 6 to <12 years

Genvoya is approved by the FDA to treat children aged 6 to <12 years and weighing ≥25 kg based on a 24-week safety study in 23 children. There were no study discontinuations due to medication toxicity, but at Week 24 the participants’ CD4 T lymphocyte (CD4) cell counts had decreased by median of 130 cells/mm$^3$ (with a range of 472–266 cells/mm$^3$), and CD4 percent decreased by a median of 2.1% (with a range of 8.4% to 5.9%). Stribild is not FDA-approved for use in children weighing <25 kg.

References


