



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Cobicistat (COBI, TYBOST) (Last updated March 1, 2016; last reviewed March 1, 2016)

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

Formulations

Tablets: 150 mg

Fixed-Dose Combination Tablets:

- [Stribild] Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus TDF 300 mg
- [Genvoya] Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus TAF 10 mg
- [Evotaz] Atazanavir 300 mg plus cobicistat 150 mg
- [Prezcobix] Darunavir 800 mg plus cobicistat 150 mg

Dosing Recommendations

Cobicistat is a Pharmacokinetic (PK) Enhancer:

- The only use of cobicistat is in adolescents and adults as a PK enhancer (boosting agent) of selected protease inhibitors (PIs) and the integrase inhibitor elvitegravir. Cobicistat is **not** interchangeable with ritonavir. See dosing information for specific PIs and elvitegravir that require cobicistat for boosting.

Pediatric Dosing

Not **Food and Drug Administration (FDA)**-Approved for Use in Children Aged <18 years:

- Cobicistat alone (as Tybost)
- Stribild
- Evotaz
- Prezcobix

Not FDA-Approved for Use in Children Aged <12 Years or Weighing <35 kg:

- Genvoya

Adolescent and Weighing ≥35 kg

- Cobicistat 150 mg orally once daily as a component of Genvoya

Adult (Aged ≥18 Years) Dose:

- Cobicistat must be administered as
 - The combination tablet Stribild or Genvoya, in which case it would not be dosed with any other antiretroviral (ARV) drugs; *or*
 - **The tablet Tybost** co-administered with atazanavir or darunavir at the doses listed in the table below and at the same time, in **combination with other ARV drugs; *or***
 - Combination tablets with atazanavir (Evotaz) or darunavir (Prezcobix), with food, and in

Selected Adverse Events

- When co-administered with TDF, cobicistat may be associated with higher risk of renal tubular adverse events than ritonavir.

Special Instructions

- Cobicistat is not interchangeable with ritonavir.
- Do not administer cobicistat with ritonavir or with drugs containing cobicistat.
- Not recommended for use with more than one ARV that requires PK enhancement (e.g., elvitegravir in combination with a PI) because no data are available.
- Use with PIs other than atazanavir 300 mg or darunavir 800 mg administered once daily is not recommended because no data are available on other combinations or doses.
- Patients with a confirmed increase in serum creatinine >0.4 mg/dL from baseline should be closely monitored for renal safety.
- When used in combinations with TDF, monitor serum creatinine, urine protein, and urine glucose at baseline and every 3 to 6 months while on therapy ([see Table 12i](#)). In patients at risk of renal impairment, also monitor serum phosphate.
- **When used in combination with other ARV drugs, see those specific sections of the appendix (atazanavir, darunavir, elvitegravir, TDF, TAF).**

Metabolism/Elimination

- Cytochrome P (CYP) 3A4 and CYP2D6 inhibitor
- Cobicistat inhibits renal tubular secretion of

combination with other ARV drugs.

Cobicistat Dose	Co-administered Agent Dose	Patient Population
150 mg orally once daily	As part of Stribild or Genvoya; no other ARV drugs needed	Treatment-naive or treatment-experienced with virus susceptible to all ARV drug components of Stribild or Genvoya
150 mg orally once daily	Atazanavir 300 mg (co-formulated as Evotaz or given as a separate drug) orally once daily plus other ARV drugs	Treatment-naive or treatment-experienced
150 mg orally once daily	Darunavir 800 mg (co-formulated as Prezcofix or given as a separate drug) orally once daily plus other ARV drugs	Treatment-naive or treatment-experienced with no darunavir-associated resistance mutations

creatinine, increasing the serum creatinine concentration (and **decreasing** estimated glomerular filtration rate) without decreasing actual glomerular function.

Dosing of Cobicistat in Patients with Renal Impairment:

- 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 because dose adjustments required for emtricitabine and TDF cannot be achieved with a fixed-dose combination tablet.
- Genvoya should not be initiated in patients with estimated CrCl <30 mL/min.
- Neither Stribild nor Genvoya should 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](#) and <http://www.hiv-druginteractions.org/>)

- **Metabolism:** Cobicistat is an inhibitor of CYP3A4 and a weak inhibitor of CYP2D6; in addition, cobicistat inhibits adenosine triphosphate (ATP)-dependent transporters BCRP and P-glycoprotein and the organic anion transporting polypeptides OAT1B1 and OAT1B3. **By inhibiting P-glycoprotein intestinal secretion, cobicistat increases the bioavailability of tenofovir alafenamide (TAF) by 2.2-fold, so the 10-mg dose of TAF in Genvoya is equivalent to the 25-mg dose of TAF found in other coformulated, TAF-containing preparations not containing cobicistat.**^{1,2} The potential exists for multiple drug interactions when using cobicistat.
- Before cobicistat is administered, a patient’s medication profile should be carefully reviewed for potential interactions and overlapping toxicities with other drugs.
- Cobicistat and ritonavir are not interchangeable, and administration with either atazanavir or darunavir may result in different drug interactions when used with other concomitant medications.

Major Toxicities

- **More common:** Nausea, vomiting, diarrhea, abdominal pain, anorexia
- **Less common (more severe):** New onset or worsening of renal impairment when used with tenofovir disoproxil fumarate. Rhabdomyolysis; increased amylase and lipase.

Resistance

Not applicable: cobicistat has no antiviral activity. Its sole use is as a pharmacokinetic enhancer of antiretroviral drugs.

Pediatric Use

Approval

Cobicistat alone (as Tybost), or cobicistat co-formulated with atazanavir (as Evotaz) or darunavir (as PrezcoBix), or as a component of Stribild, is not Food and Drug Administration (FDA)-approved for use in children aged <18 years. Cobicistat as a component of Genvoya is FDA-approved at the adult dose in children aged ≥ 12 years and body weight ≥ 35 kg. The safety of cobicistat as a component of Genvoya in this age and weight group suggests the cobicistat component would be safe in other formulations as well.³

References

1. Ruane PJ, DeJesus E, Berger D, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of tenofovir alafenamide as 10-day monotherapy in HIV-1-positive adults. *J Acquir Immune Defic Syndr*. 2013;63(4):449-455. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23807155>.
2. Lepist EI, Phan TK, Roy A, et al. Cobicistat boosts the intestinal absorption of transport substrates, including HIV protease inhibitors and GS-7340, in vitro. *Antimicrob Agents Chemother*. 2012;56(10):5409-5413. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22850510>.
3. Cobicistat (Tybost) [package insert]. Food and Drug Administration. 2014. Available at http://www.gilead.com/~media/Files/pdfs/medicines/hiv/tybost/tybost_pi.pdf. Accessed February 10, 2016.