Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Downloaded from https://aidsinfo.nih.gov/guidelines on 6/30/2018

Visit the AIDSinfo website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at https://aidsinfo.nih.gov/e-news.
Cobicistat (COBI, TYBOST) (Last updated May 22, 2018; last reviewed May 22, 2018)

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

Formulations
Tablets: 150 mg

Fixed-Dose Combination Tablets:
- [Stribild] Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus tenofovir disoproxil fumarate (TDF) 300 mg
- [Genvoya] Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus tenofovir alafenamide (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 as a PK enhancer (boosting agent) of selected protease inhibitors (PIs) and selected integrase inhibitors. Cobicistat is not interchangeable with ritonavir. See dosing information for elvitegravir and specific PIs 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)
- Evotaz
- Prezcobix
- Some members of the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV regard the above agents as potentially appropriate for use in select children aged <18 years and weighing ≥35 kg. An expert in pediatric HIV infection should be consulted.

Not FDA-Approved for Use in Children Aged <6 Years or Weighing <25 kg:
- Genvoya

Not FDA-Approved for Use in Children Aged <12 years Weighing <35 kg:
- Stribild

Child and Adolescent (Weighing ≥25 kg) Dose:
- Cobicistat 150 mg orally once daily as a component of Genvoya

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 drug 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 combination with TDF, monitor serum creatinine, urine protein, and urine glucose at baseline and every 3 to 6 months while on therapy (see Table 15i). 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
**Drug Interactions** (see also the Adult and Adolescent Guidelines and HIV Drug Interaction Checker)

- **Metabolism:** Cobicistat is an inhibitor of cytochrome P (CYP) 3A4 and a weak inhibitor of CYP2D6. In addition, cobicistat inhibits adenosine triphosphate-dependent transporters, breast cancer resistance protein, and P-glycoprotein (Pgp), and the organic anion transporting polypeptides OAT1B1 and OAT1B3. By inhibiting Pgp 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 that do not contain cobicistat. 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.

- **While cobicistat and ritonavir are both strong inhibitors of CYP3A4,** they are not interchangeable, and administration with either atazanavir or darunavir may result in different drug interactions. Darunavir induces cobicistat clearance and leads to a shorter cobicistat half-life; atazanavir decreases cobicistat clearance and increases cobicistat half-life.

<table>
<thead>
<tr>
<th>Cobicistat Dose</th>
<th>Co-Administered Agent Dose</th>
<th>Patient Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg orally once daily</td>
<td>As part of Stribild or Genvoya; no other ARV drugs needed</td>
<td>Treatment-naive or treatment-experienced with virus susceptible to all ARV drug components of Stribild or Genvoya</td>
</tr>
<tr>
<td>150 mg orally once daily</td>
<td>Atazanavir 300 mg (coformulated as Evotaz or given as a separate drug) orally once daily plus other ARV drugs</td>
<td>Treatment-naive or treatment-experienced</td>
</tr>
<tr>
<td>150 mg orally once daily</td>
<td>Darunavir 800 mg (coformulated as Prezcobix or given as a separate drug) orally once daily plus other ARV drugs</td>
<td>Treatment-naive or treatment-experienced with no darunavir-associated resistance mutations</td>
</tr>
</tbody>
</table>

- **P-glycoprotein and breast cancer resistance protein inhibitor**
  - Cobicistat inhibits renal tubular secretion of creatinine, increasing the serum creatinine concentration (and decreasing estimated glomerular filtration rate) without decreasing actual glomerular function.

Cobicistat Dosing 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.

Adolescent (Weighing ≥35 kg and SMR 4 or 5) Dose:
- Cobicistat 150 mg orally once daily as a component of Stribild

Adult (Aged ≥18 Years) Dose:
- Cobicistat must be administered as:
  - The combination tablets 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 combination with other ARV drugs.
• Cobicistat is a stronger Pgp inhibitor than ritonavir and therefore has a greater effect than ritonavir on intestinal absorption of drugs that are metabolized by Pgp, like dabigatran. Cobicistat boosts dolutegravir concentrations to a greater extent than ritonavir, presumably also due to a Pgp interaction.

• Dexamethasone induces CYP3A4 and decreases cobicistat half-life, potentially decreasing concentrations of the antiretroviral (ARV) drugs that cobicistat is boosting. Cobicistat inhibits the clearance of corticosteroids whose exposures are significantly increased by CYP3A4 inhibitors (e.g., fluticasone), potentially leading to adrenal suppression or Cushing syndrome.

**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 ARV drugs.

**Pediatric Use**

*Approval*

Cobicistat alone (as Tybost), or cobicistat coformulated with atazanavir (as Evotaz) or darunavir (as PrezcoBix), or as a component of Stribal, 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 ≥6 years and weighing ≥25 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.

**References**


