Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Cobicistat (COBI, Tybost) (Last updated April 16, 2019; last reviewed April 16, 2019)

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

Formulations

Tablet: 150 mg

Fixed-Dose Combination Tablets:
- [Evotaz] Atazanavir 300 mg/cobicistat 150 mg
- [Genvoya] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide (TAF) 10 mg
- [Prezcobix] Darunavir 800 mg/cobicistat 150 mg
- [Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg
- [Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/TAF 10 mg

Dosing Recommendations

Cobicistat is a Pharmacokinetic Enhancer:
- The only use of cobicistat is as a pharmacokinetic (PK) enhancer (boosting agent) for certain protease inhibitors (PIs) and integrase inhibitors. Cobicistat is not interchangeable with ritonavir.

Use of Cobicistat-Containing Drugs in Children and Adolescents

Not Food and Drug Administration (FDA)-Approved for Use in Children and Adolescents Aged <18 Years:
- Cobicistat alone (as Tybost)
- Evotaz
- Prezcobix
- Symtuza
- Some members of the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) regard the above agents as potentially appropriate for use in certain children aged <18 years and weighing ≥35 kg. An expert in pediatric HIV infection should be consulted before using these drugs in these patients. See the atazanavir and darunavir sections for additional information.

FDA-Approved for Use in Children and Adolescents Weighing ≥25 kg:
- Genvoya

FDA-Approved for Use in Children and Adolescents Aged ≥12 and Weighing ≥35 kg:
- Stribild
- The Panel recommends using Stribild only in patients with sexual maturity ratings of 4 or 5.

Selected Adverse Events

- Cobicistat is an inhibitor of renal tubular transporters of creatinine. This increases serum creatinine and reduces estimated glomerular filtration rate, with no change in glomerular function.

Special Instructions

- Cobicistat 150 mg is not interchangeable with ritonavir, but it has a PK boosting effect that is comparable to ritonavir 100 mg.
- Drug interactions may differ between ritonavir and cobicistat, because cobicistat is a stronger P-glycoprotein inhibitor and lacks some of the induction effects of ritonavir.
- Genvoya, Stribild, and Symtuza are approved for use in treatment-naive patients. They can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of these single-tablet regimens.
- Do not administer cobicistat with ritonavir or with FDC tablets that contain cobicistat.
- Not recommended for use with more than one ARV drug that requires PK enhancement (e.g., elvitegravir used in combination with a PI).
- Use with PIs other than once-daily atazanavir 300 mg or darunavir 800 mg is not recommended.
- Patients with a confirmed increase in serum
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Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and HIV Drug Interaction Checker)

- **Metabolism:** Metabolism of cobicistat is mainly via cytochrome P450 (CYP) 3A4 and, to a lesser degree, CYP2D6. Cobicistat is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. Cobicistat also inhibits the breast cancer resistance protein, P-glycoprotein (P-gp), the organic anion transporting polypeptides OATP1B1 and OATP1B3, and multidrug and toxin extrusion 1. Unlike ritonavir, cobicistat does not demonstrate any enzyme-inducing effects. 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.

- **Nucleoside reverse transcriptase inhibitors:** Cobicistat is a strong P-gp inhibitor; thus, a dose of tenofovir alafenamide (TAF) 10 mg combined with cobicistat produces tenofovir exposures that are similar to those produced by TAF 25 mg without cobicistat.

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**Adult (Aged ≤18 Years) Dose**

**Cobicistat Must be Administered as:**

- The fixed-dose combination (FDC) tablets Stribild, Genvoya, or Symtuza, which are complete regimens and should not be administered with any other antiretroviral (ARV) drugs; or
- The tablet Tybost, which should be administered at the same time as atazanavir or darunavir at the doses listed in the table below and used in combination with other ARV drugs; or
- The FDC tablets Evotaz (which also contains atazanavir) or Prezempix (which also contains darunavir). Both FDC tablets should be administered with food and in combination with other ARV drugs.

**Doses for Cobicistat and Coadministered Antiretroviral Drugs**

<table>
<thead>
<tr>
<th>Cobicistat Dose</th>
<th>Coadministered Agent Dose</th>
<th>Patient Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg orally once daily</td>
<td>As part of Stribild, Genvoya, or Symtuza</td>
<td>Treatment-naive or treatment-experienced, with virus that is susceptible to all ARV drug components of Stribild, Genvoya, or Symtuza</td>
</tr>
<tr>
<td>150 mg orally once daily</td>
<td>Atazanavir 300 mg (coformulated as Evotaz or given as a separate drug) given orally once daily</td>
<td>Treatment-naive or treatment-experienced</td>
</tr>
<tr>
<td>150 mg orally once daily</td>
<td>Darunavir 800 mg (coformulated as Prezempix or given as a separate drug) given orally once daily</td>
<td>Treatment-naive or treatment-experienced, with no darunavir-associated resistance mutations</td>
</tr>
</tbody>
</table>

- When using cobicistat in combination with TDF, monitor serum creatinine, urine protein, and urine glucose at baseline and every 3 months to 6 months while the patient is receiving therapy (see Table 15i). In patients who are at risk of renal impairment, serum phosphate should also be monitored.

- When using cobicistat in combination with other ARV drugs, or when using FDC tablets that contain cobicistat, see other drug sections for special instructions and additional information about the individual drug components (e.g., atazanavir, darunavir, elvitegravir, TDF, TAF).

**Metabolism/Elimination**

- Cobicistat is a strong inhibitor of cytochrome P450 (CYP) 3A4 and a weak inhibitor of CYP2D6.

**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. The dose adjustments required for emtricitabine and TDF in these patients cannot be achieved with an FDC tablet.
- Neither Genvoya nor Symtuza should be initiated in patients with estimated CrCl <30 mL/min.
- Stribild, Genvoya, and Symtuza should not be used in patients with severe hepatic impairment.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and HIV Drug Interaction Checker)

- **Metabolism:** Metabolism of cobicistat is mainly via cytochrome P450 (CYP) 3A4 and, to a lesser degree, CYP2D6. Cobicistat is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. Cobicistat also inhibits the breast cancer resistance protein, P-glycoprotein (P-gp), the organic anion transporting polypeptides OATP1B1 and OATP1B3, and multidrug and toxin extrusion 1. Unlike ritonavir, cobicistat does not demonstrate any enzyme-inducing effects. 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.

- **Nucleoside reverse transcriptase inhibitors:** Cobicistat is a strong P-gp inhibitor; thus, a dose of tenofovir alafenamide (TAF) 10 mg combined with cobicistat produces tenofovir exposures that are similar to those produced by TAF 25 mg without cobicistat.
• **Non-nucleoside reverse transcriptase inhibitors:** Efavirenz, etravirine, and nevirapine should not be used with cobicistat.

• **Protease inhibitors:** Using cobicistat as a dual booster for elvitegravir and darunavir has been studied in people with HIV and people without HIV, and the evidence is conflicting. When elvitegravir plus cobicistat plus darunavir was administered to people without HIV, the $C_{\text{trough}}$ concentration of elvitegravir was 50% lower than the $C_{\text{trough}}$ concentration seen in people who received elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (TDF) without darunavir.2 When elvitegravir/cobicistat/emtricitabine/TAF was administered with darunavir to patients with HIV, both darunavir and elvitegravir concentrations were comparable to historic controls.1

• **Integrase inhibitors:** In one small study, dolutegravir $C_{\text{trough}}$ concentrations were higher when dolutegravir was administered with darunavir/cobicistat (DRV/c) than when it was administered with darunavir/ritonavir.4 Bictegravir area under the curve increases 74% when bictegravir is administered with DRV/c.5 Increased serum concentrations of corticosteroids can occur when corticosteroids and cobicistat are coadministered; this can lead to clinically significant adrenal suppression. Adrenal suppression occurs regardless of whether the corticosteroids are administered orally or by some other route (e.g., intranasal, inhaled, interlaminar) and regardless of whether the corticosteroids are administered routinely or intermittently. A possible exception is beclomethasone, which appears to be a relatively safe option with inhaled or intranasal administration.4

**Major Toxicities**

• **More common:** Nausea, vomiting, diarrhea, abdominal pain, anorexia.

• **Less common (more severe):** New onset renal impairment or worsening of renal impairment when used with TDF. Rhabdomyolysis; increased amylase and lipase levels.

**Resistance**

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

**Pediatric Use**

**Approval**

The Food and Drug Administration (FDA) has not approved the use of cobicistat alone (as Tybost), cobicistat coformulated with atazanavir (as Evotaz) or darunavir (as Prezcobix), or cobicistat as a component of Symtuza in children aged <18 years. Cobicistat, as a component of Stribild, is approved by the FDA at the adult dose for use in children and adolescents aged ≥12 years and weighing ≥35 kg. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends limiting use to those with a sexual maturity rating of 4 or 5. Cobicistat, as a component of Genvoya, is approved by the FDA at the adult dose for use in children weighing ≥25 kg.

**References**


