Selected Properties of Cobicistat

Other names	GS-9350, Tybost® Combination formulation: • Stribild® (elvitegravir/cobicistat/emtricitabine/tenofovir) • Prezcobix® (darunavir 800 mg/cobicistat 150 mg); Rezolsta® (EU trade name)
Manufacturer	Gilead Sciences Canada Inc. (Stribild®, Tybost®); Janssen Inc (Prezcobix®)
Pharmacology/Mechanism of Action	Potent, mechanism-based inhibitor of the P450 CYP3A family. Molecular weight 776.02.
Activity	Cobicistat has no detectable antiviral activity in cell culture against HIV-1, HBV, or HCV and does not antagonize the antiviral activity of elvitegravir, emtricitabine, or tenofovir.
Effect of Food	When administered as a fixed dose combination tablet (elvitegravir 150 mg, emtricitabine 200 mg, tenofovir 300 mg, cobicistat 150 mg) in healthy volunteers, cobicistat AUC_{inf} and C_{max} each ↑ 3% with a light meal, and ↓ 17% and 24% respectively with a high-fat meal. NB: elvitegravir AUC_{inf} and C_{max} ↑ by 34% and 22%, respectively, with a light meal and by 87% and 56% with a high-fat meal.[German et al. 2010] Take cobicistat with food.
Protein Binding	97-98% Mean blood:plasma ratio is approximately 0.5.
Vd	77 L
Tmax	3 hours
serum T ½	3.5 hours (when administered as Stribild®)
Drug Concentrations	Following oral administration, systemic exposure is almost exclusively parent drug. When administered as a fixed dose combination (elvitegravir 150 mg, emtricitabine 200 mg, tenofovir 300 mg, cobicistat 150 mg) in HIV-infected subjects, mean cobicistat AUC 8.3 ± 3.8 ug.h/mL, Ctrough 0.05 ± 0.13 ug/mL, Cmax 1.1 ± 0.4 ug/mL. When administered as a single agent 150 mg tablet formulation, mean cobicistat AUC 11788.86 ng.h/mL, Ctau 58.29 ng/mL, Cmax 1557.73 ng/mL. <u>Pediatric formulations</u>: Cobicistat pediatric formulations, administered as either 50 mg tablets or 20 mg dispersible tablets were each bioequivalent to the adult cobicistat tablet formulation in healthy adult subjects.[Custodio et al. 2014]
CSF (% of serum)	In rats, minimal transport of cobicistat across blood:brain and blood:testes barriers was observed.

Metabolism	Extensively metabolized via CYP3A4 and 2D6 (minor).
Excretion	Primarily eliminated in the feces (86%). Renal elimination is a minor pathway (<10% of a dose).
Dosing – Adult	Prezcobix®: 1 tablet daily with food. Stribild®: 1 tablet daily with food. Tybost®: 150 mg cobistat with 300 mg atazanavir
Dosing – Pediatric	The pharmacokinetics of cobicistat in pediatric subjects (<18 years of age) have not been established.
Special instructions for pediatric patients	
Adjust in Liver Dysfunction	**Tybost®:** No dose adjustment of cobicistat is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Cobicistat has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). **Prezcobix®:** There are no pharmacokinetic data regarding the use of Prezcobix® in patients with hepatic impairment. The safety and efficacy of Prezcobix® have not been established in patients with severe hepatic insufficiency. Darunavir and cobicistat are metabolized by the liver. Studies with darunavir/ritonavir and with cobicistat single agent suggest no dose adjustment is required in patients with mild or moderate hepatic impairment. **Stribild®:** No dose adjustment of Stribild® is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of Stribild® in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, Stribild® is not recommended for use in patients with severe hepatic impairment. The pharmacokinetics of elvitegravir 150 mg/cobicistat 150 mg QD for 10 days were compared in HIV-negative subjects with normal and moderately impaired hepatic function (Child-Pugh Class B). Elvitegravir AUC, Cmax and Ctau were 35% ↑ , 41%% ↑ and 80% ↑ and cobicistat AUC, Cmax were unaffected and Ctau was 108% ↑, respectively, in subjects with hepatic impairment vs. normal hepatic function. These changes are not considered clinically relevant, and dose adjustment is not required in patients with mild to moderate hepatic impairment.[Custodio et al. 2014]
Adjust in Renal Failure/Dialysis	**Cobicistat** does not require dosage adjustment required for renal impairment, including severe renal impairment. Cobicistat should not be initiated as part of a regimen containing emtricitabine, lamivudine, tenofovir disoproxil fumarate or adefovir in patients who have an estimated creatinine clearance below 70 mL/min since dose adjustment of these drugs is required below 50 mL/min and such dose adjustments have not been established in combination with cobicistat. **Prezcobix®:** No dose adjustment is required in patients with renal impairment. Prezcobix® should not be initiated as part of a

	regimen containing emtricitabine, lamivudine, tenofovir disoproxil fumarate or adefovir in patients who have an estimated creatinine clearance below 70 mL/min since dose adjustment of these drugs is required below 50 mL/min and such dose adjustments have not been established in combination with Prezcobix®. **Stribild®:** Since Stribild® is a fixed-dose combination tablet which also contains tenofovir and emtricitabine, Stribild® should not be initiated in patients with estimated creatinine clearance <70 mL/min. Stribild® should be discontinued if estimated creatinine clearance declines below 50 mL/ min during treatment as dose interval adjustment required for emtricitabine and tenofovir disoproxil fumarate (tenofovir DF) cannot be achieved. The pharmacokinetics of elvitegravir 150 mg/cobicistat 150 mg QD for 7 days were compared in HIV-negative subjects with severe renal impairment (eGFR < 30 mL/min) vs. those with normal renal function (eGFR ≥ 90 mL/min). Elvitegravir AUC, Cmax and Ctau were 25% ↓, 33% ↓ and 31% ↓ and cobicistat AUC, Cmax and Ctau were 25% ↑, 22% ↑ and 13% ↑, respectively, in subjects with renal impairment vs. normal renal function. Mean eGFR ↓ 11% in the renal impairment group and ↓ 9% in the normal renal function group at day 7 relative to day 1; mean eGFR returned to baseline by day 14; these decreases attributed to transient inhibition of proximal tubular secretion of creatinine by cobicistat.[German et al. 2012] As cobicistat is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis.
Toxicity	Most common adverse drug reactions (to Stribild®) are nausea and diarrhea (incidence greater than or equal to 10%, all grades). Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. An increase in serum creatinine due to cobicistat's inhibitory effect generally does not exceed 0.4 mg per dL (35.36 µmol/L) from baseline. In Study 114, decreases in estimated creatinine clearance occurred early in treatment with cobicistat, after which they stabilized. The mean (± SD) change in estimated glomerular filtration rate (eGFR) by Cockcroft-Gault method after 48 weeks of treatment was -13.4 ± 15.2 mL/min in the cobicistat -boosted atazanavir + tenofovir/FTC group and -8.7 ± 14.5 mL/min in the ritonavir-boosted atazanavir + tenofovir/FTC group. Effects reported with tenofovir or Stribild® include new onset or worsening renal impairment, and decreases in bone mineral density. Avoid administering Stribild® with concurrent or recent use of nephrotoxic drugs. NB: Lactic acidosis and severe hepatomegaly with steatosis,

	including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate, a component of Stribild®.
Pregnancy & Lactation	Pregnancy category B. Studies in rats have demonstrated that cobicistat is secreted in milk. It is not known whether cobicistat is excreted in human milk.
Drug Interactions	Cobicistat is an inhibitor of CYP3A and CYP2D6, as well as the transporters p-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3. Thus, coadministration of Stribild® with drugs that are primarily metabolized by CYP3A or CYP2D6, or are substrates of P-gp, BCRP, OATP1B1 or OATP1B3 may result in increased plasma concentrations of such drugs. Cobicistat exerts no significant inhibition of 1A2, 2C9 or 2C19. Cobicistat 150 mg exhibits similar CYP3A4 inhibiting effect as ritonavir 100 mg. The inhibitory effects of cobicistat on CYP3A function will persist for approximately 7-10 days following discontinuation.
Baseline Assessment	Assess creatinine clearance (CLcr), urine glucose and urine protein before initiating treatment with Stribild®. Test for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued emtricitabine or tenofovir DF, two of the components of Stribild®.
Routine Labs	Cobicistat inhibits tubular secretion of creatinine and causes modest increases in serum creatinine and modest declines in estimated creatinine clearance; in healthy volunteers, administration of cobicistat for 7 days was associated with a lower estimated GFR (onset in days, reversibility in days). Cobicistat had no effect on actual GFR [Cohen et al. 2010]. Patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg per dL from baseline should be closely monitored for renal safety.
Dosage Forms	Tybost®: 150 mg tablet, DIN 02411423 Stribild®: fixed dose combination of elvitegravir 150 mg, emtricitabine 200 mg, tenofovir 300 mg, cobicistat 150 mg green capsule-shaped, film-coated tablet, DIN: 02397137 Prezcobix®: fixed dose combination of darunavir 800 mg and cobicistat 150 mg pink oval-shaped, film-coated tablet, DIN 02426501
Storage	Store at 25C (or between 15 and 30C) in original container.

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