## Selected Properties of Elvitegravir

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<th>Other names</th>
<th>GS-9137, JTK-303, EVG, Vitekta®</th>
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<td>Combination formulation:</td>
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  - Stribild® (elvitegravir/cobicistat/emtricitabine/tenofovir) |
| Manufacturer | Gilead Sciences |
| Pharmacology/Mechanism of Action | Elvitegravir inhibits the strand transfer activity of HIV-1 integrase (integrase strand transfer inhibitor; INSTI), an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the integration of HIV-1 DNA into host genomic DNA, blocking the formation of the HIV-1 provirus and propagation of the viral infection. Elvitegravir does not inhibit human topoisomerases I or II. Molecular weight: 447.9 |
| Activity | Preclinical pharmacokinetic studies have demonstrated potent anti-HIV activity in vitro with a serum free IC\text{50} of 0.2 nM and an EC\text{90} in peripheral blood mononuclear cells of 12 nM. It has shown additive to synergistic activity with all other antiretrovirals. In vitro effects on HIV-1 clinical isolates: mean EC\text{50} of 0.62 nM. Elvitegravir displays antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC\text{50} values ranged from 0.1 to 1.3 nM) and activity against HIV-2 (EC\text{50} value of 0.53 nM). Elvitegravir does not show inhibition of replication of HBV or HCV in cell culture. |
| Resistance - genotypic | HIV-1 isolates with reduced susceptibility to elvitegravir have been selected in cell culture. Reduced susceptibility to elvitegravir was associated with the primary integrase substitutions T66A/I, E92G/Q, S147G, and Q148R. Additional integrase substitutions observed in cell culture selection included D10E, S17N, H51Y, F121Y, S153F/Y, E157Q, D232N, R263K, and V281M. |
| Resistance - phenotypic | In treatment-naive HIV-1 infected subjects:  
  - Failure isolates expressing primary elvitegravir resistance-associated substitutions (N=11) had median decreases in susceptibility to elvitegravir of 44-fold (range: 6- to greater than 198-fold) and 33-fold (range: 4- to greater than 122-fold) compared to wild-type reference HIV-1 and to the respective baseline isolates, respectively. Most subjects (N=10) who developed integrase substitutions associated with elvitegravir resistance also developed the M184I/V RT substitutions, conferring reduced susceptibility to both elvitegravir and emtricitabine. |
| Cross-Resistance | In preclinical studies, this compound has been found to be fully active against nucleoside-, non-nucleoside- and PI-resistant isolates. Cross-resistance has been observed among INSTIs. |
Elvitegravir-resistant viruses showed varying degrees of cross-resistance in cell culture to raltegravir depending on the type and number of substitutions in HIV-1 integrase. Among the four primary elvitegravir resistance-associated substitutions detected in the STRIBILD-treatment virologic failure isolates, E92Q, Q148R, and N155H individually conferred reduced susceptibility both to elvitegravir (greater than 32-fold) and raltegravir (greater than 5-fold) when introduced into a wild-type virus by site-directed mutagenesis. The T66I substitution conferred greater than 14-fold reduced susceptibility to elvitegravir but less than 3-fold to raltegravir. Among the three primary raltegravir resistance-associated substitutions (Y143H/R, Q148H/K/R, and N155H), all but one (Y143H) conferred significant reductions in susceptibility to elvitegravir (greater than 5-fold).

### Oral Bioavailability

**Effect of Food**

When administered as a fixed dose combination tablet with emtricitabine, tenofovir and cobicistat in healthy volunteers, elvitegravir AUC\text{inf} and C_{\text{max}} \uparrow by 34\% and 22\%, respectively, with a light meal (~373 kcal, 20\% fat) and by 87\% and 56\% with a high-fat meal (~800 kcal, 50\% fat).[German et al. ICAAC 2009]

Take fixed dose combination tablet with food.

**Protein Binding**

Approximately 98.8\% protein bound. The mean blood-to-plasma ratio is 0.73.

**Vd**

**T\text{max}**

4 hours (when administered as Stribild®)

**serum T \frac{1}{2}**

12.9 hours (when administered as Stribild®).

After single dose administration of [14C] elvitegravir coadministered with 100 mg ritonavir, 94.8 \% and 6.7 \% of the administered dose was excreted in feces and urine, respectively.

### Drug Concentrations

After single dose elvitegravir 50 mg/ritonavir 100 mg in 8 healthy male volunteers: elvitegravir C_{\text{max}} 321 (30.2\% CV) ng/mL, AUC\text{inf} 5430 ng.hr/mL (35.1\% CV).

Steady-state administration in healthy subjects:
- EVG 150/rtv 100 mg QD: C_{\text{trough}} 448 ng/mL
- EVG 300/rtv 100 mg QD: C_{\text{trough}} 502 ng/mL

When administered as a fixed dose combination (elvitegravir 150 mg, emtricitabine 200 mg, tenofovir 300 mg, cobicistat 150 mg) in HIV-infected subjects, mean elvitegravir AUC 23.0 ± 7.5 ug.h/mL, C_{\text{trough}} 0.45 ± 0.26 ug/mL, C_{\text{max}} 1.7 ± 0.4 ug/mL.

In a randomized study comparing the relative bioavailability and kinetics of elvitegravir 150/emtricitabine 200/tenofovir 300/cobicistat 150 mg fixed-dose tablet versus elvitegravir 150/ritonavir 100 mg plus tenofovir/emtricitabine in 42 healthy subjects, high EVG C_{\text{trough}} and clinically equivalent tenofovir and FTC exposures were achieved with the fixed-dose tablet relative to ritonavir-boosted EVG.[German et al. JAIDS 2010]
No clinically relevant pharmacokinetic differences have been observed between men and women for cobicistat-boosted elvitegravir, emtricitabine and tenofovir DF.

In adolescents (ages 12-17):
Administration of fixed-dose elvitegravir/cobicistat/tenofovir/FTC yielded plasma concentrations within the range of historical adult exposures: elvitegravir AUC ↑ 30%, Cmax ↑ 42%, emtricitabine AUC ↑ 20%, tenofovir AUC ↑ 37% compared to adults. These differences not expected to result in different safety or efficacy profile.[Gaur et al. 2014]

Elvitegravir pediatric tablets & suspension:
Elvitegravir pediatric tablets and suspension are bioequivalent to adult elvitegravir tablet (all boosted with ritonavir) in healthy adult subjects.[Custodio et al. 2014]

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<th>Minimum target trough concentrations (for wildtype virus)</th>
<th>Protein-adjusted, in vitro IC50: 7.17 ng/mL</th>
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<tr>
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<td>Protein-adjusted, in vitro IC95: 44.9 ng/mL</td>
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<td>Estimated IQ of elvitegravir 50/rtv 100 mg dose: 18.8 based on IC50.</td>
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| CSF (% of serum)            | 95% dose excreted via feces |

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<th>Metabolism</th>
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<td>The majority of elvitegravir metabolism is mediated by CYP3A enzymes. Elvitegravir also undergoes glucuronidation via UGT1A1/3 enzymes.</td>
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<td>Elvitegravir is a modest 2C9 inducer.</td>
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<th>Excretion</th>
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<td>95% dose excreted via feces</td>
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<th>Dosing – Adult</th>
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<td>Stribild®: 1 tablet daily with food.</td>
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<td>Elvitegravir: 85 mg daily if taken with concomitant atazanavir/ritonavir or lopinavir/ritonavir; 150 mg daily if taken with concomitant darunavir/ritonavir, fosamprenavir/ritonavir, or tipranavir/ritonavir</td>
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<th>Dosing – Pediatric</th>
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<td>The pharmacokinetics of elvitegravir or cobicistat in pediatric subjects (&lt;18 years of age) have not been established.</td>
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<th>Special instructions for pediatric patients</th>
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<td>Adjust in Liver Dysfunction</td>
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| 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]
| No dose adjustment of Stribild® is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. |
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.

### Adjust in Renal Failure/Dialysis

Elvitegravir and cobicistat do not require dosage adjustment required for renal impairment. However, 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]

The renal safety of Stribild® or cobicistat (with darunavir 800 mg or atazanavir 300 mg) was assessed in subjects with mild-moderate renal impairment (eGFR 50-89 mL/min).[Post et al. 2013] At 48 weeks follow-up, no cases of proximal renal tubulopathy occurred in the Stribild®-treated subjects.[Szwarcberg et al. 2014]

### Toxicity

Most common adverse drug reactions (to Stribild®) are nausea and diarrhea (incidence greater than or equal to 10%, all grades).

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. Elvitegravir is excreted in human breast milk.

### Drug Interactions

Elvitegravir absorption is reduced 45% when administered simultaneously with antacids; separate dosing from antacids or vitamin or mineral supplements containing calcium, zinc or iron
by at least 2 hours. Elvitegravir may be administered simultaneously with proton-pump inhibitors and H2-blockers.

Stribild® can alter the concentration of drugs metabolized by CYP3A or CYP2D6. Drugs that induce CYP3A can alter the concentrations of one or more components of Stribild®.

Elvitegravir (in Stribild®) should not be used in conjunction with protease inhibitors or non-nucleoside reverse transcriptase inhibitors due to potential drug-drug interactions including altered and/or suboptimal pharmacokinetics of cobicistat, elvitegravir, and/or the coadministered antiretroviral products. Stribild® should not be administered concurrently with products containing ritonavir or regimens containing ritonavir due to similar effects of cobicistat and ritonavir on CYP3A.

Coadministration of Stribild® is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. Elvitegravir (Stribild®) is also contraindicated with strong CYP3A inducers, which may lead to decreased exposure and possible loss of efficacy.

See separate “Drug interactions with Integrase Inhibitors” table.

**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**

- Monitor CLcr, urine glucose, and urine protein in all patients.
- Monitor serum phosphorus in patients at risk for renal impairment.
- Cobicistat may cause modest increases in serum creatinine and modest declines in estimated creatinine clearance without affecting renal glomerular function. 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.
- Consider monitoring bone mineral density (BMD) in patients with a history of pathologic fracture or other risk factors of osteoporosis or bone loss.

**Dosage Forms**

- Vitekta®: 85 mg (DIN 02411172) and 150 mg (DIN 02411180) tablets.
- Combination formulation:
  - Stribild®: elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate
300 mg, DIN 02397137
- green, capsule-shaped, film-coated, debossed with “GSI” on one side and the number “1” surrounded by a square box (1) on the other side

**Storage**
Store at 25C (or between 15 and 30C) in original container.

**References:**


