Selected Properties of Elvitegravir

Other names	GS-9137, JTK-303, EVG, Vitekta® Combination formulation: • 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_{50} of 0.2 nM and an EC_{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 EC50 of 0.62 nM. Elvitegravir displays antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC50 values ranged from 0.1 to 1.3 nM) and activity against HIV-2 (EC50 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-naïve 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_{inf} and C_{max} ↑ 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	
Tmax	4 hours (when administered as Stribild®)
serum T ½	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 Cmax 321 (30.2% CV) ng/mL, AUCinf 5430 ng.hr/mL (35.1% CV). Steady-state administration in healthy subjects: • EVG 150/rtv 100 mg QD: Ctrough 448 ng/mL • EVG 300/rtv 100 mg QD: Ctrough 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, Ctrough 0.45 ± 0.26 ug/mL, Cmax 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 Ctrough 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. <u>In adolescents (ages 12-17):</u> Administration of fixed-dose elvitegravir/cobicistat/tenofovir/FTC yielded plasma concentrations within the range of historical adult exposures: elvitegravir AUC ↑ 30%, Cmax ↑ 42%, emtrictabine 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]
Minimum target trough concentrations (for wildtype virus)	Protein-adjusted, in vitro IC50: 7.17 ng/mL Protein-adjusted, in vitro IC95: 44.9 ng/mL Estimated IQ of elvitegravir 50/rtv 100 mg dose: 18.8 based on IC50.
CSF (% of serum)	
Metabolism	The majority of elvitegravir metabolism is mediated by CYP3A enzymes. Elvitegravir also undergoes glucuronidation via UGT1A1/3 enzymes. Elvitegravir is a modest 2C9 inducer.
Excretion	95% dose excreted via feces
Dosing – Adult	Stribild®: 1 tablet daily with food. 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
Dosing – Pediatric	The pharmacokinetics of elvitegravir or cobicistat in pediatric subjects (<18 years of age) have not been established.
Special instructions for pediatric patients	
Adjust in Liver Dysfunction	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. 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:

Custodio JM, Rhee M, Shen G et al. Pharmacokinetics and safety of boosted-elvitegravir in subjects with hepatic impairment. Antimicrob Agents Chemother. 2014 Feb 18. [Epub ahead of print].

Custodio JM, Liu Y, Graham H, et al. Bioequivalence of two pediatric formulations vs adult tablet formulation of elvitegravir [abstract]. Conference on Retroviruses and Opportunistic Infections, Boston MA, March 3-6, 2014.

Gaur A, Fourie J, Chokephaibulkit K et al. Pharmacokinetics, efficacy and safety of an integrase inhibitor-based single-tablet regimen in HIV-Infected treatment-naïve adolescents [abstract]. Conference on Retroviruses and Opportunistic Infections, Boston MA, March 3-6, 2014.

German P et al. Effect of food on pharmacokinetics of elvitegravir, emtricitabine, tenofovir and the pharmacoenhancer GS-9350 as a fixed dose combination tablet [abstract A1-1300]. 49th Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco, CA, September 12-15, 2009.

German P, Warren D, West S, Hui J, Kearney BP. Pharmacokinetics and bioavailability of an integrase and novel pharmacoenhancer-eontaining single-tablet fixed-dose combination regimen for the treatment of HIV. J Acquir Immune Defic Syndr 2010 Jul 30. [Epub ahead of print]

German P, Wei X, Mizuno V, Cheng A, Kearney B, Mathias A. Pharmacokinetics of elvitegravir and cobicistat in subjects with severe renal impairment [abstract P_38]. 13th International Workshop on Clinical Pharmacology of HIV Therapy, April 16-18th, 2012, Barcelona, Spain.

Gilead Sciences. Stribild® (elvitegravir/cobicistat/emtricitabine/tenofovir) Prescribing Information. Foster City, CA. August 2012.

Post FA, Winston J, Andrade-Villanueva JF, et al. Elvitegravir/cobicistat/emtricitabine/tenofovir DF in HIV-infected patients with mild to moderate renal impairment. J Acquir Immune Defic Syndr. 2014 Dec 2. [Epub ahead of print]

Ramanthan S, Wright M, West S, Kearney BP. Pharmacokinetics, metabolism and excretion of ritonavir-boosted GS-9137 (elvitegravir) [abstract 30]. 8th International Workshop on Clinical Pharmacology of HIV Therapy. Budapest, Hungary, April 16-18, 2007.

Ramanathan S, West, S, Hui J, Chuck SL, Kearney BP. Clinical pharmacokinetics of once-daily elvitegravir boosted by atazanavir versus ritonavir [abstract O18]. 9th International Workshop on Clinical Pharmacology of HIV Therapy. New Orleans, USA, April 7-9, 2008.

Szwarcberg J et al. Elvitegravir/Cobicistat/Emtricitabine/Tenofovir DF (STB) in HIV-Infected Patients with Mild to Moderate Renal Impairment [abstract]. 20th International AIDS Conference, Melbourne, Australia, July 20-25, 2014.