Selected Properties of Dolutegravir

Other names	Tivicay®, S/GSK 1349572 Combination formulation: • Triumeq®: abacavir/dolutegravir/lamivudine
Manufacturer	ViiV Healthcare
Pharmacology/Mechanism of Action	Dolutegravir is a novel HIV-1 integrase strand transfer inhibitor. The bulk drug is a sodium salt of dolutegravir with a molecular weight of 441.36 g/mol. Dolutegravir inhibits HIV integrase strand transfer, with an IC_{50} of 2.7 nM and 12.6 nM. Inhibition of integrase prevents the covalent insertion, or integration, of unintegrated linear HIV-1 DNA into the host cell genome preventing the formation of the HIV-1 provirus.
Activity	• HIV 1- EC_{50}: 0.5 to 2.1 nM (in vitro) • HIV 1 - diverse, clinical isolates EC_{50}: 0.02 to 2.14 nM (in vitro) • HIV 2- EC_{50}: 0.09 to 0.61 nM (in vitro)
Resistance - genotypic	Resistance data are preliminary and limited. Dolutegravir has the ability to readjust its binding position and thus allows for an enhanced genetic barrier to resistance. Resistance is associated with mutations at position 148 (Q148H/R) plus ≥ 2 additional substitutions including L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R.
Resistance - phenotypic	Studies of dolutegravir activity in patients with known INSTI-resistant mutations have been favourable, indicating that dolutegravir retains activity in a variety of INSTI-resistant phenotypes.
Cross-Resistance	The single INSTI- resistance substitutions T66K, I151L, and S153Y conferred a >2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a >2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold). Viruses with integrase inhibitor resistance mutations remain fully sensitive to the effects of non-nucleoside reverse transcriptase inhibitors as well as nucleosides and protease inhibitors.
Oral Bioavailability	The absolute bioavailability of dolutegravir has not been established.
Effect of Food	Dolutegravir may be taken with or without food. Food increased the extent of absorption and slowed the rate of absorption of dolutegravir. Low-, moderate-, and high-fat meals increased dolutegravir AUC(0-∞) by 33%, 41%, and 66% and increased Cmax by 46%, 52%, and

	67%.[Song et al. 2011] **Dolutegravir may be administered daily or twice daily without regard to meals.** Similarly, the effect of food on plasma pharmacokinetics of a fixed-dose tablet of dolutegravir, abacavir and lamivudine was similar to prior food effects observed on the kinetics of dolutegravir administered as a single agent and of abacavir/lamivudine administered as a fixed dose combination.[Weller et al. 2014]
Protein Binding	≥ 98.9% protein bound
Vd	Estimated 17.4 L following 50-mg once-daily administration.
Tmax	Dolutegravir is rapidly absorbed with T_{max} 2 hours in the fasted state. Low-, moderate-, and high-fat meals prolonged T_{max} to 3, 4 and 5 hours respectively.
serum T ½	Terminal half-life of approximately 13- 14 hours
Drug Concentrations	Dolutegravir plasma concentrations increased in a less than dose-proportional manner above 50 mg. Bioequivalence of a fixed dose combination of dolutegravir 50 mg, abacavir 600 mg and lamivudine 300 mg compared to dolutegravir administered as a single agent and abacavir/lamivudine administered as a combined agent.[Weller et al. 2013] <u>Children:</u> At doses of ~1 mg/kg once daily, adequate mean AUC and C24 were achieved in HIV-infected children between 6-11 years of age.[Viani et al. 2014] <u>Cervicovaginal fluid (CVF) concentrations</u> A total of 8 healthy females given DTG 50 mg daily for 5–7 days had 11 paired blood plasma (BP) and cervicovaginal fluid (CVF) samples collected over 24 h following the first dose (PK1) and multiple dosing (PK2). Each woman underwent cervical tissue (CT) and vaginal tissue (VT) biopsies at 1/4 time points at PK1 and PK2. After single and multiple dosing, CVF concentrations were approximately 6% of blood plasma exposure with low inter-individual variability. After multiple dosing, CT and VT exposures were 9-10% of blood plasma concentrations. After multiple dosing, DTG accumulated to a greater extent in tissue than in blood plasma or CVF, suggesting increased tissue affinity.[Adams et al. 2014] <u>Colorectal tissue concentrations</u> Following single dose, colorectal tissue concentrations were approximately 18 % of plasma concentrations.[Greener et al. 2013]
Minimum target trough concentrations (for wildtype virus)	Protein-adjusted 90% inhibitory concentration (IC_{90}) of dolutegravir for wild-type virus is 0.064 µg/ml

CSF (% of serum)	In 11 treatment-naïve subjects on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 18 ng/mL (range: 4 ng/mL to 232 ng/mL) 2 to 6 hours postdose after 2 weeks of treatment. The clinical relevance of this finding has not been established.
Metabolism	Dolutegravir is not an inhibitor of cytochrome P450 enzymes, major UGTs, or P-glycoprotein and does not induce CYP3A. It is primarily metabolized via UGT1A1 with some contribution from CYP3A
Excretion	Feces 53% (dolutegravir unchanged) Urine: 31% (dolutegravir glucuronide 18.9% + metabolite 3% + hydrolytic N-dealkylation product 3.6%)
Dosing – Adult	**<u>Tivicay®:</u>** **Treatment-naïve or treatment experienced INSTI-naïve:** 50 mg daily with or without food **Co-administered with potent UGT1A/CYP3A inducers OR INSTI-associated resistance:** 50 mg twice daily with or without food Dolutegravir film-coated tablets must be swallowed whole. **<u>Triumeq®:</u>** 1 tablet daily with or without food (treatment-naïve or treatment experienced INSTI-naïve only)
Dosing – Pediatric	**Treatment naïve, 12 years of age and older and weighing at least 40 kg:** 50 mg daily **Co-administered with potent UGT1A/CYP3A inducers** (efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir or rifampin)**:** 50 mg twice daily Findings from the IMPAACT P1093 study support the selection of a 50 mg dolutegravir dose in children 12 to <18 years of age weighing at least 40 kg.[Hazra et al. 2012] The safety and effectiveness of dolutegravir in pediatric patients less than 12 years of age, weighing less than 40 kg and who are INSTI-experienced with documented or suspected resistance to other INSTIs have not been established.
Adjust in Liver Dysfunction	Dolutegravir is primarily metabolized and eliminated by the liver. In a trial comparing 8 subjects with moderate hepatic impairment (Child-Pugh Score B) with 8 matched healthy controls, exposure of dolutegravir from a single 50-mg dose was similar between the 2 groups**. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh Score A or B)**. [Song et al. 2013]

	The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied. Therefore, **dolutegravir is not recommended for use in patients with severe hepatic impairment.**
Adjust in Renal Failure/Dialysis	Renal clearance of unchanged drug is a minor pathway of elimination for dolutegravir. In a trial comparing 8 subjects with severe renal impairment (CrCl <30 mL/min) with 8 matched healthy controls, AUC, Cmax, and C24 of dolutegravir were decreased by 40%, 23%, and 43%, respectively, compared with those in matched healthy subjects. The cause of this decrease is unknown. These changes are not considered clinically significant.[Weller et al. 2013] Population pharmacokinetic analysis using data from SAILING and VIKING-3 trials indicated that mild and moderate renal impairment had no clinically relevant effect on the exposure of dolutegravir. **No dosage adjustment is necessary for treatment-naïve or treatment-experienced and INSTI-naïve patients with mild, moderate, or severe renal impairment or for INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance) with mild or moderate renal impairment**. **Caution is recommended for INSTI-experienced patients with severe renal impairment as the decreased dolutegravir exposure may lead to loss of therapeutic effect.** Dolutegravir has not been studied in patients on dialysis. Given its non-renal clearance and high plasma protein binding (~99%), dialysis would not be expected to affect dolutegravir pharmacokinetics. NB: TRIUMEQ™ should not be used in patients with creatinine clearance of less than 50 mL/min; while no dosage adjustment of dolutegravir or abacavir is necessary in patients with renal impairment, dose reduction is required for the lamivudine component. As dosage reduction is not possible with TRIUMEQ™, the separate preparations of dolutegravir (TIVICAY™), abacavir (ZIAGEN®), and lamivudine (3TC®) should be used.
Toxicity	• Hypersensitivity reactions have been reported, characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. Discontinue dolutegravir and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. • During the clinical studies of dolutegravir in adults, the most common moderate-to-severe adverse reactions were insomnia and headache • Worsening or new transaminase elevations in patients with

	underlying hepatitis B or C • May be associated with fat redistribution and immune reconstitution syndrome
Overdose	• Single doses up to 250 mg have been studied in healthy subjects without evidence of toxicity • No known specific treatment for overdose with dolutegravir • It is unlikely to be significantly removed by dialysis due to high protein binding
Pregnancy & Lactation	*Pregnancy* • Reproduction studies performed in rats and rabbits at doses up to 27 times the human dose of 50 mg twice daily and have revealed no evidence of impaired fertility or harm to the fetus *Lactation* • It is not know if dolutegravir is secreted in human milk. • Dolutegravir is secreted in the milk of lactating rats. • It is recommended that HIV infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV
Drug Interactions	*See Drug interaction tables for more details* Dolutegravir should be administered 2 hours before or 6 hours after taking medications containing polyvalent cations (Mg, Al, Fe, Ca) *Effect of Dolutegravir on the Kinetics of Other Agents* • Inhibits OCT2 *in vitro* Does NOT inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, UGT1A1, UGT2B7, P-gp, BRCP, OATP1B1, OATP1B3, OCT1 or MRP2 *in vitro* • Does NOT induce CYP1A2, CYP2B6, or CYP3A4 *in vitro* *Effect of Other Agents on the Pharmacokinetics of Dolutegravir* • Strong inducers of UGT1A1 (ex Rifampin) will reduce plasma concentrations of dolutegravir • Strong inhibitors of UGT1A1 (Ex ATV/r) will increase plasma concentrations of dolutegravir • Strong inducers of UGT1A3, UGT1A9, BCRP, and P-gp may decrease dolutegravir plasma concentration in vitro
Baseline Assessment	CD4, viral load
Routine Labs	CD4, viral load
Dosage Forms	Tivicay®: 50 mg tablets, bottles of 30. DIN 02414945. Yellow, round, film-coated, biconvex tablets debossed with SV 572 on one side and 50 on the other side Triumeq®: abacavir 600mg, dolutegravir 50mg and lamivudine 300mg. DIN 02430932. Purple, oval, film-coated, biconvex tablets debossed with “572 Trı” on one side.
Storage	Store at room temperature 25°C; excursions permitted 15° to 30°C

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