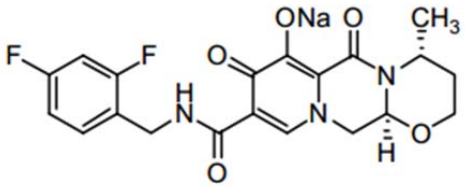
Dolutegravir PK Fact Sheet

Details

Generic Name	Dolutegravir
Trade Name	Tivicay®
Class	Integrase Inhibitor
Molecular Weight	441.36
Structure	

Summary of Key Pharmacokinetic Parameters

Linearity/non-linearity	Dolutegravir plasma concentrations increased in a less than dose-proportional manner above 50 mg. Non-linear exposure of dolutegravir was observed following 50 mg twice daily compared with 50 mg once daily in HIV-1–infected subjects and was attributed to the use of metabolic inducers in the background antiretroviral regimens of subjects receiving dolutegravir 50 mg twice daily in clinical trials.
Steady state	~5 days
Plasma half life	~14 h
Cmax	3.67 µg/ml (50 mg once daily, determined from population PK analyses in HIV+ subjects) 4.15 µg/ml (50 mg twice daily, determined from population PK analyses in HIV+ subjects)
Cmin	1.11 µg/ml (50 mg once daily, determined from population PK analyses in HIV+ subjects) 2.12 µg/ml (50 mg twice daily, determined from population PK analyses in HIV+ subjects)
AUC	53.6 µg.h/ml (50 mg once daily, determined from population PK analyses in HIV+ subjects) 75.1 µg.h/ml (50 mg twice daily, determined from population PK analyses in HIV+ subjects)
Bioavailability	Not determined.
Absorption	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 by 33%, 41%, and 66%; increased Cmax by 46%, 52%, and 67%; and prolonged Tmax to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively.
Protein Binding	≥98.9%
Volume of Distribution	17.4 L (50 mg once daily, determined from population PK analyses in HIV+ subjects)
CSF:Plasma ratio	In 11 treatment-naïve subjects on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 18 ng/mL (range: 4-232 ng/mL) 2 to 6 h post dose after 2 weeks of treatment. The clinical relevance of this finding has not been established.
Semen:Plasma ratio	<7% of blood plasma exposure (and below the protein adjusted IC90) [1]
Renal Clearance	31% of the total oral dose was excreted in urine, represented by an ether glucuronide of dolutegravir (18.9% of total dose), a metabolite formed by oxidation at the benzylic carbon (3% of total dose), and its hydrolytic N-dealkylation product (3.6% of total dose). Renal elimination of unchanged drug was low (<1% of the dose)

Renal Impairment	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. Population pharmacokinetic analysis 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 warranted for INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance with severe renal impairment, as the decrease in dolutegravir concentrations may result in loss of therapeutic effect and development of resistance to TIVICAY or other coadministered antiretroviral agents. Dolutegravir has not been studied in patients requiring dialysis.
Hepatic Impairment	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). 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.

Metabolism and Distribution

Metabolised by	Primarily glucuronidation via UGT1A1 with some contribution from CYP3A. Also a substrate of UGT1A3, UGT1A9, in vitro.
Inducer of	Does not induce CYP1A2, CYP2B6, or CYP3A4
Inhibitor of	In vitro inhibitor of OCT2 (IC50 = 1.93 µM) Does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, UGT1A1, UGT2B7, P-gp, BCRP, OATP1B1, OATP1B3, OCT1, or MRP2.
Transported by	BCRP and P-gp

References

Unless otherwise stated (see below), information is from:
Tivicay Summary of Product Characteristics, ViiV Healthcare UK Ltd.
Tivicay US Prescribing Information, ViiV Healthcare.

1. Greener BN, Patterson KB, Prince HM, et al. Dolutegravir pharmacokinetics in the genital tract and colorectum of HIV-negative men after single and multiple dosing. *J Acquir Immune Defic Syndr*, 2013, **64(1):** 39-44.