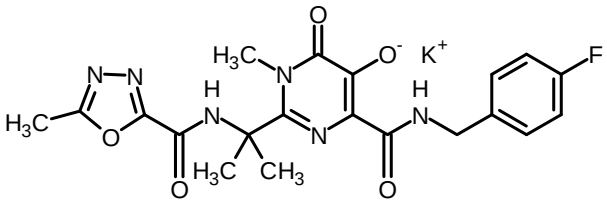
Raltegravir PK Fact Sheet

Details

Generic Name	Raltegravir
Trade Name	Isentress®
Class	Integrase Inhibitor
Molecular Weight	482.51
Structure	

Summary of Key Pharmacokinetic Parameters

Linearity/non-linearity	AUC and Cmax increase dose proportionally over the dose range 100-1600 mg. C12h increases dose proportionally over 100-800 mg and increases slightly less than dose proportionally over 100-1600 mg. Dose proportionality has not been established in patients.
Steady state	With twice-daily dosing, steady state is achieved within approximately the first 2 days of dosing.
Plasma half life	~9 h
Cmax	2.17 µg/ml (400 mg twice daily) [1]
Cmin	68.6 ng/ml (400 mg twice daily) [1]
AUC	6.91 µg/ml.h
Bioavailability	Absolute bioavailability has not been established.
Absorption	Raltegravir may be administered with or without food and was administered without regard to food in the pivotal safety and efficacy studies in HIV-infected patients. Administration of multiple doses of raltegravir following a moderate-fat meal did not affect raltegravir AUC to a clinically meaningful degree with an increase of 13% relative to fasting. Raltegravir C12h was 66% higher and Cmax was 5% higher following a moderate-fat meal compared to fasting. Administration of raltegravir following a high-fat meal increased AUC and Cmax by approximately 2-fold and increased C12h by 4.1-fold. Administration of raltegravir following a low-fat meal decreased AUC and Cmax by 46% and 52%, respectively; C12h was essentially unchanged. Food appears to increase pharmacokinetic variability relative to fasting.
Protein Binding	~83%
Volume of Distribution	Unknown
CSF:Plasma ratio	In a study of HIV-1 infected subjects (n=18) who received raltegravir 400 mg twice daily, the median cerebrospinal fluid raltegravir concentration was 5.8% (range 1 to 53.5%) of the corresponding plasma concentration. This median proportion was approximately 3-fold lower than the free fraction of raltegravir in plasma. The clinical relevance of this finding is unknown.
Semen:Plasma ratio	Unknown
Renal Clearance	~32% of total dose (9% as unchanged drug, 23% as glucuronide conjugate).
Renal Impairment	Renal clearance of unchanged medicinal product is a minor pathway of elimination. Clinically important pharmacokinetic differences between patients with severe renal insufficiency and healthy subjects have not been observed. No dosage adjustment is required for patients with renal impairment.
Hepatic Impairment	No dosage adjustment is required in mild to moderate hepatic impairment. The safety and efficacy of raltegravir have not been established in severe underlying liver disorders and should be used with caution in these patients.

Metabolism and Distribution

Metabolised by	Mainly via UGT1A1-mediated glucuronidation. No CYP450 involvement.
Inducer of	No CYP450 or P-glycoprotein involvement expected.
Inhibitor of	No CYP450 or P-glycoprotein involvement expected.
Transported by	Unknown

References

Unless otherwise stated (see below), information is from:
Isentress® Summary of Product Characteristics, Merck Sharp & Dohme Ltd.
Isentress® US Prescribing Information, Merck Sharp & Dohme.

1. Markowitz M, Morales-Ramirez J, *et al*. Antiretroviral activity, pharmacokinetics, and tolerability of MK-0518, a novel inhibitor of HIV-1 Integrase, dosed as monotherapy for 10 days in treatment-naive HIV-1–infected individuals. *J Acquir Immune Defic Syndr*, 2006; 43(5): 509-515.