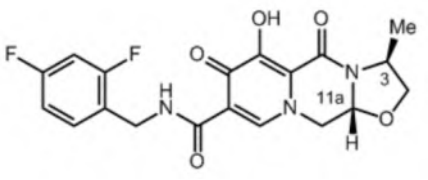
Cabotegravir (IM) PK Fact Sheet

Details

Generic Name	Cabotegravir
Trade Name	Vocabria®; Cabenuva® (co-packaged with rilpivirine)
Class	Integrase Inhibitor
Molecular Weight	405.35
Structure	

Summary of Key Pharmacokinetic Parameters

Linearity/non-linearity	Plasma cabotegravir exposure increases in proportion or slightly less than in proportion to dose following single and repeat IM injection of doses ranging from 100 to 800 mg.
Steady state	Following a single intramuscular dose, plasma cabotegravir concentrations are detectable on the first day and gradually rise to reach maximum plasma concentration with a median Tmax of 7 days. Pharmacokinetic steady-state is achieved by 44 weeks.
Plasma half life	~5.6 to 11.5 weeks Residual concentrations of cabotegravir may remain in the systemic circulation of patients for prolonged periods (up to 12 months or longer).
Cmax	4.2 µg/ml (400 mg IM monthly) 4.0 µg/ml (600 mg IM every 2 months)
Ctau	2.8 µg/ml (week 48 data for a 1-month interval following 400 mg IM monthly) 1.6 µg/ml (week 48 data for a 2-month interval following 600 mg IM every 2 months)
AUC	2415 µg.h/ml (400 mg IM monthly) 3764 µg.h/ml (600 mg IM every 2 months)
Bioavailability	The absolute bioavailability of cabotegravir has not been established.
Absorption	Cabotegravir injection exhibits absorption rate-limited kinetics (i.e., flip-flop pharmacokinetics) resulting from slow absorption from the gluteal muscle into the systemic circulation resulting in sustained plasma concentrations.
Protein Binding	>99.8
Volume of Distribution	12.3L (following oral administration)
CSF:Plasma ratio	0.003
Semen:Plasma ratio	Not evaluated in humans
Renal Clearance	27%; 0% as unchanged drug (following oral administration)

Dosing in Renal and Hepatic Impairment

Renal Impairment

No clinically important pharmacokinetic differences between subjects with severe renal impairment (CrCL <30 mL/min and not on dialysis) and matching healthy subjects were observed. No dosage adjustment is necessary for patients with mild to severe renal impairment (not on dialysis). Cabotegravir has not been studied in patients with end-stage renal disease on renal replacement therapy. As cabotegravir is greater than 99% protein bound, dialysis is not expected to alter exposures of cabotegravir. If administered in a patient on renal replacement therapy, cabotegravir should be used with caution.

Hepatic Impairment

No clinically important pharmacokinetic differences between subjects with moderate hepatic impairment and matching healthy subjects were observed. 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 cabotegravir has not been studied. If administered in a patient with severe hepatic impairment, cabotegravir should be used with caution.

Metabolism and Distribution

Metabolised by

Primarily UGT1A1, with a minor contribution from UGT1A9.

Simulations using PBPK modeling show that no clinically significant interaction is expected during coadministration of cabotegravir with drugs that inhibit UGT1A1.

Medicinal products which are strong inducers of UGT1A1 or UGT1A9 are expected to decrease cabotegravir plasma concentrations leading to lack of efficacy.

Inducer of

In vitro, cabotegravir did not induce CYP1A2, CYP2B6, or CYP3A4.

Inhibitor of

In vivo, oral cabotegravir did not have an effect on midazolam, a CYP3A4 probe.

In vitro, cabotegravir inhibited renal OAT1 (IC50=0.81 µM) and OAT3 (IC50=0.41 µM). Based on physiologically based pharmacokinetic (PBPK) modeling, cabotegravir may increase the AUC of OAT1/3 substrates up to approximately 80%. Therefore, caution is advised when co-dosing with OAT1/3 substrates with a narrow therapeutic index.

Cabotegravir is not a clinically relevant inhibitor of the following enzymes and transporters: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B4, UGT2B7, UGT2B15, and UGT2B17, P-gp, BCRP, BSEP, OCT1, OCT2, OATP1B1, OATP1B3, MATE 1, MATE 2-K, MRP2 or MRP4.

Transported by

Cabotegravir is a substrate of P-gp and BCRP, however, because of its high permeability, no alteration in absorption is expected when coadministered with either P-gp or BCRP inhibitors.

In vitro, cabotegravir was not a substrate of OATP1B1, OATP1B3 or OCT1.

References

Unless otherwise stated (see below), information is from:
Vocabria® Summary of Product Characteristics, ViiV Healthcare.
Cabenuva® US Prescribing Information, ViiV Healthcare.