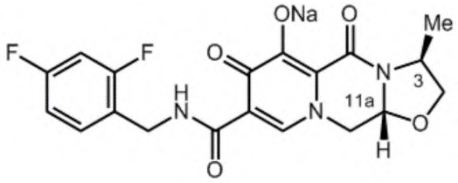
Cabotegravir (oral) PK Fact Sheet

Details

Generic Name	Cabotegravir
Trade Name	Vocabria®
Class	Integrase Inhibitor
Molecular Weight	427.34 (as cabotegravir sodium)
Structure	

Summary of Key Pharmacokinetic Parameters

Linearity/non-linearity	There were dose-proportional increases in AUC, Cmax and Ctau, and Cmin over a 5-30 mg dose range with both single and repeat dose oral administration [1].
Steady state	With once daily dosing, pharmacokinetic steady-state is achieved by 7 days.
Plasma half life	41 h
Cmax	8.0 µg/ml
Ctau	4.6 µg/ml
AUC	145 µg/h/ml
Bioavailability	The absolute bioavailability of cabotegravir has not been established.
Absorption	Cabotegravir tablets may be taken with or without food. When taken at the same time as rilpivirine tablets, cabotegravir tablets should be taken with a meal. Food increased the extent of absorption of cabotegravir: high fat meals increased cabotegravir AUC and Cmax both by 14% relative to fasted conditions. These increases are not clinically significant.
Protein Binding	>99.8
Volume of Distribution	12.3L
CSF:Plasma ratio	0.003 (following IM administration)
Semen:Plasma ratio	Not evaluated in humans
Renal Clearance	27%; 0% as unchanged drug

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). The effect of end-stage renal disease (CrCL <15 mL/min) on the pharmacokinetics of cabotegravir is unknown. Cabotegravir has not been studied in patients on dialysis. 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, 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.
Vocabria® US Prescribing Information, ViiV Healthcare.

1. Spreen W, Min S, Ford SL, et al. Pharmacokinetics, safety, and monotherapy antiviral activity of GSK1265744, an HIV integrase strand transfer inhibitor. HIV Clin Trials. 2013 Sep-Oct;14(5):192-203.