Metabolic Considerations and Drug-Drug Interactions with *Apretude* When Used as Pre-Exposure Prophylaxis

Summary

- *Apretude* (long-acting cabotegravir, CAB LA) is a substrate of UGT1A1 with some contribution from UGT1A9.[1,2]
  - Drugs that are strong inducers and inhibitors of UGT1A1 or UGT1A9 may affect plasma concentrations of CAB.[3,4]
- CAB is not an inhibitor or an inducer of UGT1A1 or CYP3A4.[3,4]
- Use of CAB with rifampin (rifampicin), rifapentine, carbamazepine, oxcarbazepine, phenobarbital, and phenytoin is contraindicated
- Apretude (long-acting cabotegravir, CAB LA) is not affected by absorption related drug-drug interactions in the gastrointestinal tract because it is administered by intramuscular injection.
- Important Safety Information and Boxed Warning can be found in the Prescribing Information and can also be accessed from the Our HIV Medicines section of viivhealthcare.com/us.

To access additional scientific information related to ViiV Healthcare medicines, visit the ViiV US Medical Portal at viivhcmedinfo.com.

No drug interaction studies have been conducted with CAB LA.[2] Since the pathways of metabolism and elimination are independent of formulation type, the data from oral CAB have been extrapolated to identify drugs with which use of CAB LA may cause an interaction.[2,4-11]

METABOLISM OF CABOTEGRAVIR

CAB is primarily metabolized by UGT1A1 with some contribution from UGT1A9.[1] Drugs that are strong inducers of UGT1A1 or 1A9 are expected to decrease CAB plasma concentrations.

In vivo, CAB did not have an effect on midazolam, a CYP3A4 probe. CAB is not a clinically relevant inhibitor of the following enzymes and transporters[2]: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B4, UGT2B7, UGT2B15, and UGT2B17, P-gp, breast cancer resistance protein (BCRP), Bile salt export pump (BSEP), organic cation transporter (OCT)1, OCT2, OATP1B1, OATP1B3, multidrug and toxin extrusion transporter (MATE) 1, MATE 2-K, multidrug resistance protein (MRP) 2 or MRP4.

CAB inhibited the organic anion transporters (OAT) 1 (IC50=0.81 µM) and OAT3 (IC50=0.41 µM) *in vitro*, however, based on physiologically based pharmacokinetic (PBPK) modelling no interaction with OAT substrates is expected at clinically relevant concentrations.[2]

In vitro, CAB did not induce CYP1A2, CYP2B6, or CYP3A4.[2]

Based on these data and the results of drug interaction studies, CAB is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.[2]

CONTRAINDICATIONS

The drugs with which use of CAB LA are contraindicated are listed in Table 1.

Table 1. Drugs Contraindicated with CAB LA[1,10]

Drug Class	Contraindicated Drugs in Class	Effect on Concentration
Anticonvulsants	Carbamazepine, Oxcarbazepine, Phenobarbital, and Phenytoin	↓CAB
Antimycobacterials	Rifampicin and Rifapentine	↓CAB

↓ = Decrease; CAB = cabotegravir

OTHER POTENTIALLY SIGNIFICANT DRUG INTERACTIONS

Other potentially significant drug interactions are listed in Table 2.

Table 2. Other Potentially Significant Drug Interactions with CAB LA[1,2,11]

Drug Class	Associated Drugs in Class	Effect on Concentration	Clinical Comment
Antimycobacterial	Rifabutin	↓CAB	• Rifabutin may decrease CAB injection plasma concentrations, concomitant use should be avoided. • When rifabutin is started before or concomitantly with the first initiation injection of CAB, the recommended dosing of CAB is one 600-mg (3-mL) injection, followed 2 weeks later by a second 600-mg (3-mL) initiation injection and monthly thereafter while on rifabutin. • When rifabutin is started at the time of the second initiation injection or later, the recommended dosing schedule of CAB is 600 mg (3 mL) monthly while on rifabutin. After stopping rifabutin, the recommended dosing schedule of CAB is 600 mg (3 mL) every 2 months.

↓ = Decrease; ↔ = No change; CAB = cabotegravir

DRUGS WITH NO CLINICALLY SIGNIFICANT INTERACTIONS

Because CAB LA is administered intramuscularly, it will not be affected by absorption-related drug interactions (e.g., di- and trivalent cations, proton pump inhibitors, etc.).

Based on drug interaction study results, the following drugs can be coadministered with CAB LA (non-antiretrovirals) or given after discontinuation of CAB LA (antiretrovirals and non-antiretrovirals) without a dose adjustment: etravirine, midazolam, oral contraceptives containing levonorgestrel and ethinyl estradiol, and rilpivirine.[3,4,6,8,9]

For inquires on interactions with other drugs that are not listed herein, it is recommended to consult a reputable drug interaction websites, such as http://www.hiv-druginteractions.org/checker.

This information is scientific and non-promotional in nature and is not intended for further distribution.

This information is not intended to offer recommendations for using this product in a manner inconsistent with its approved labeling. Please consult the Prescribing Information. For ViiV Healthcare to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 877-844-8872.

Selection of references follows principles of evidence-based medicine and, therefore, references may not be all inclusive.

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