Cabotegravir (CAB)

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Summary

- Pharmacokinetic (PK) data are insufficient to make dosing recommendations for oral cabotegravir (CAB) or long-acting (LA) injectable cabotegravir (CAB-LA) during pregnancy or breastfeeding.
- Clinical data are insufficient to characterize the risk for congenital anomalies associated with *in utero* exposure to CAB. No reproductive toxicity or teratogenicity concerns were identified in animal studies.

Human Studies in Pregnancy

Pharmacokinetics

No studies have been conducted on the PK of CAB and rilpivirine (RPV) with ongoing intramuscular (IM) injections during pregnancy. Clinical trial data reported to date are limited to pregnant women who stopped receiving CAB injections for the treatment or prevention of HIV once pregnancy was recognized and began an alternative oral antiretroviral regimen throughout the remainder of their pregnancies. From the Phase 2b/3/3b clinical trials of long-acting injectable CAB and RPV for the treatment of HIV, PK data are available for seven of the nine participants exposed to long-acting injectable CAB and RPV therapy with live birth outcomes. Plasma concentrations were within the range of observed concentrations of nonpregnant women who discontinued long-acting injectable CAB and RPV.[1] In HPTN 084, which assessed the efficacy and safety of CAB-LA for HIV prevention, PK data are available in 26 participants who received at least one dose of CAB prior to the confirmation of pregnancy and discontinuation of CAB. The apparent terminal-phase half-life ($t_{1/2app}$) in pregnant participants was comparable to nonpregnant individuals, although body mass index greater than 27.2 was associated with longer CAB $t_{1/2app}$.[2] One physiologically based (PB) PK model predicted that pregnancy will have minimal influence on the PK of CAB-LA and that dose adjustments will not be indicated; the model did not specify whether CAB was initiated in pregnancy or continued from prior to pregnancy.[3] A newer PBPK model of pregnant individuals initiating long-acting injectable CAB and RPV in the early second trimester predicted a reduction in plasma concentrations of 29.5% and 23.0%, respectively, at the first trough after the first injection. After the sixth injection in the second and third trimesters, plasma concentrations were 31.1% and 29.2% lower for CAB and RPV, respectively. These reductions are attributed to the predicted induction of uridine diphosphate glucuronyl transferase 1A1 and cytochrome P450 3A4 during the second and third trimesters.[4]

Placental and Breast Milk Passage

Median (interquartile range 25–75) CAB maternal-to-fetal concentration ratio assessed using an *ex vivo*, dually perfused human cotyledon model was 10% (5–16), suggesting low placental transfer.[5] No data are available describing breast milk passage of CAB in humans.[6] See Rilpivirine for data about RPV.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry has not monitored sufficient numbers of first-trimester exposures to CAB to report on the risk of overall birth defects.[7]

In the Phase 2b/3/3b trials of CAB and RPV, 25 of 325 women of reproductive potential became pregnant while exposed to CAB and RPV (5 oral, 20 long-acting injectable), resulting in 8 elective abortions, 6 spontaneous abortions (5 in the first trimester), 1 ectopic pregnancy, and 10 live births (1 oral, 9 long-acting injectable). Of the 10 live births, 1 case of congenital ptosis was reported in a preterm infant with intrauterine growth restriction, and 1 late preterm delivery occurred due to induction of labor.[1] In HPTN 084, among 29 confirmed pregnancies (of whom 26 received at least one injection), 4 pregnancy losses occurred prior to 20 weeks, 1 occurred between 20 to 36 weeks, and 22 live births occurred. No congenital anomalies, preterm births, or drug-related maternal or neonatal adverse events have been reported to date in the live births of infants from mothers who conceived while receiving IM injections of CAB alone.[8] Increased adverse events (grade 1–3) during pregnancy were noted in the CAB arm of HPTN 084 (compared to the tenofovir disoproxil fumarate/emtricitabine arm) but were deemed unrelated to the study drug. See Rilpivirine for additional information about oral RPV.

Animal Studies

Carcinogenicity

CAB was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term carcinogenicity studies of CAB in mice did not show any carcinogenic potential at systemic exposures that were sevenfold (in females) or eightfold (in males) greater than human exposure at the recommended dose. In rats, no drug-related increases in tumor incidence were observed at CAB exposures up to approximately 26 times higher than those in humans at the recommended dose.[9]

CAB was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or *in vivo* rodent micronucleus assay.[10] See Rilpivirine for data about RPV.

Reproduction/Fertility

In rats, no effects on fertility were observed at CAB exposures at least 20 times greater than the exposure in humans at recommended doses. See Rilpivirine for data about RPV.

Teratogenicity/Adverse Pregnancy Outcomes

Studies in pregnant rats showed that CAB crosses the placenta and can be detected in fetal tissue. Treatment of rat dams with CAB during pregnancy and postpartum had no effects on fetal viability, although a minor decrease was observed in fetal body weight with exposures 28 times those seen in humans at the recommended dose. No drug-related fetal toxicities were observed with rat dam exposures approximately 13 times those seen in humans at the recommended dose, and no fetal malformations were observed at any rat dam dose. A delay in the onset of parturition and increases in the number of stillbirths and neonatal deaths were seen with exposure of rat dams to CAB at 28 times the human exposure with recommended doses, but not with exposure at 13 times the human exposure with recommended doses.

No drug-related fetal toxicities were observed after CAB exposures of rabbit dams of up to approximately 0.7 times those seen in humans at the recommended dose.[9]

A recent study in mouse models demonstrated decreased human embryonic stem cell counts and pluripotency and induced dysregulation of genes involved in early differentiation at subtherapeutic levels of CAB.[11] Additionally, a study of zebrafish found that although CAB did not cause gross morphological defects at low doses, pericardial edema, uninflated swim bladder, decreased heartbeats, growth delay, and decreased hatching rate were observed at the highest concentrations. At subtherapeutic doses, decreased locomotion was observed, suggesting alterations of nervous system integrity.[12] Clinical data and clinical trials data in humans are insufficient to refute or corroborate these findings.

See Rilpivirine for data about RPV.

Placental and Breast Milk Passage

Studies in lactating rats and their offspring indicate that CAB is present in rat milk. See Rilpivirine for data about RPV.

Excerpt from Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines for information about the dosing and safety of individual drug components of the FDC tablet during pregnancy.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
Cabotegravir (CAB) *Vocabria (oral)* *Apretude (injection for HIV pre-exposure prophylaxis)* (CAB) *Cabenuva* Note: CAB and RPV is a two-drug co-packaged product for IM injection.	CAB • CAB 30-mg tablets for oral administration • CAB 200-mg/mL suspension for IM injection CAB and RPV • CAB 200-mg/mL suspension for IM injection • RPV 300-mg/mL suspension for IM injection	Pregnancy *PK in Pregnancy* • No PK studies in human pregnancy *Dosing in Pregnancy* • Insufficient data to make dosing recommendations For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., RPV). Standard Adult Doses *Oral Lead-in Therapy (Optional)* • CAB (Vocabria) o One 30-mg tablet once daily in combination with RPV (Edurant) 25-mg once daily taken with a meal for 4 weeks • CAB (Apretude) o Initiation ▪ CAB 600-mg (3 mL) injections given 1 month apart for 2 consecutive months (on the last day of an oral lead-in, if used, or within 3 days) o Continuation Therapy ▪ CAB 600-mg (3 mL) injections every 2 months thereafter	No human data are available regarding placental passage. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.

Excerpt from Table 14

		• CAB and RPV (Cabenuva) o Initiation ▪ CAB 600-mg (3 mL) and RPV 900-mg (3 mL), given as two separate injections in separate ventrogluteal sites for 2 consecutive months (on the last day of an oral lead-in if used) o Continuation Therapy ▪ *Monthly:* CAB 400-mg (2 mL) and RPV 600-mg (2 mL), given as two separate injections in separate ventrogluteal sites once a month with allowance for a +/- 7-day administration window ▪ *Every 2 months:* Starting in month 4, CAB 600-mg (2 mL) and RPV 900-mg (2 mL), given as two separate injections in separate ventrogluteal sites once a month with allowance for a +/- 7-day administration window ▪ Patients should be monitored for approximately 10 minutes for post-injection reactions. A 23-gauge, 1.5-inch IM needle is recommended for the injection and is provided in the packaging. Longer, 2-inch needles should be used in patients with BMIs >30 kg/m^2. *Changing Dosing Frequency and Managing Missed Doses* • Refer to the package insert for instructions about changing the frequency of continuation doses and managing missed doses (see Apretude and Cabenuva)	

Excerpt from Table 14

[a] Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal delivery plasma drug ratio:

High: >0.6
Moderate: 0.3–0.6
Low: <0.3

Key: ARV = antiretroviral; BMI = body mass index; CAB = cabotegravir; IM = intramuscular; PK = pharmacokinetic; RPV = rilpivirine

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