Cabotegravir (Vocabria, CAB)
Cabotegravir Rilpivirine (Cabenuva, CAB RPV)

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Animal Studies

Carcinogenicity

Cabotegravir (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.[1]

CAB was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or in the *in vivo* rodent micronucleus assay.[2] See Rilpivirine for data about rilpivirine (RPV).

Reproduction/Fertility

In rats, no effects on fertility were observed at CAB exposures (area under the curve) 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.[1] 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.

Human Studies in Pregnancy

Pharmacokinetics

No studies have been conducted on the pharmacokinetics (PKs) of CAB and RPV with ongoing intramuscular (IM) injections during pregnancy. Clinical trial data reported to date are limited to pregnant women who stopped receiving CAB injections once pregnancy was recognized and began an alternative oral antiretroviral regimen throughout the remainder of their pregnancies. CAB PK data are available for three pregnant women after cessation of injections. In two of these women, both of whom maintained typical weight through delivery, CAB concentrations were predicted to remain therapeutic. Also, the rate of decline in concentrations during pregnancy in these two women was similar to the rate of decline in non-pregnant adults. The third pregnant woman had a faster rate of decline in CAB concentrations than expected; this woman had a low body mass index (BMI) (15.3 kg/m2), and her low body fat may have had altered absorption from the long-acting depot injection site.[3]

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.[4] No data are available describing breast milk passage of CAB in humans. See Rilpivirine for data about RPV.

Teratogenicity/Adverse Pregnancy Outcomes

No congenital anomalies, preterm birth, or drug-related maternal or neonatal adverse events have been reported to date in the four live births of infants from mothers who conceived while receiving IM injections of CAB and RPV. See Rilpivirine for additional information about oral RPV.

Excerpt from Table 11

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 11 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)*(CAB RPV) *Cabenuva* CAB 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 RPV** • CAB 200 mg/mL suspension for IM injection • RPV 300 mg/mL suspension for IM injection	**Standard Adult Doses** *Oral Lead-in Therapy* *CAB (Vocabria)* • One 30-mg tablet once daily **in combination with RPV** (Edurant) 25 mg once daily taken with a meal for 4 weeks *CAB (Apretude)* *Initiation:* • CAB 600 mg (3 mL) injection given 1 month apart for 2 consecutive months on the last day of an oral lead-in if used or within 3 days *Continuation Therapy* • CAB 600 mg (3mL) injections every 2 months thereafter *CAB RPV (Cabenuva)* *Loading Dose to Be Given on Last Day of Oral Therapy:* • CAB 600 mg (3 mL) and RPV 900 mg (3 mL), given as two separate injections in separate ventrogluteal sites *Continuation Therapy* • 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 • Patients should be monitored for ~10 minutes for post-injection reactions. A	No human data are available regarding placental passage. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
		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. **Pregnancy** *PKs 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).	

[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 11).

[b] Placental transfer categories are determined by mean or median cord blood/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; FDC = fixed-dose combination; IM = intramuscular; PK = pharmacokinetic; RPV = rilpivirine

References

1. Cabotegravir and Rilpivirine (cabenueva kit) [package insert]. Food and Drug Administration. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212888s000lbl.pdf.

2. Edurant (Rilpivirine) [package insert]. Food and Drug Administration. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202022s014lbl.pdf.

3. Patel P, Thiagarajah S, Ford S, et al. Cabotegravir pharmacokinetic tail in pregnancy and neonatal outcomes. Abstract 775. Presented at: Conference on Retroviruses and Opportunistic Infections. 2020. Boston, MA. Available at: https://www.croiconference.org/abstract/cabotegravir-pharmacokinetic-tail-in-pregnancy-and-neonatal-outcomes/.

4. Pencole L, Le MP, Bouchet-Crivat F, Duro D, Peytavin G, Mandelbrot L. Placental transfer of the integrase strand inhibitors cabotegravir and bictegravir in the ex-vivo human cotyledon perfusion model. *AIDS*. 2020;34(14):2145-2149. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32796211.