Abacavir (Ziagen, ABC)

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Animal Studies

Carcinogenicity

Abacavir (ABC) has been found to be mutagenic and clastogenic in some *in vitro* and *in vivo* assays. In long-term carcinogenicity studies in mice and rats, malignant tumors of the preputial gland of males and the clitoral gland of females were observed in both species, and malignant hepatic tumors and nonmalignant hepatic and thyroid tumors were observed in female rats. The tumors were seen in rodents at exposures that were six to 32 times those observed in humans who received the recommended dose.[1]

Reproduction/Fertility

No effect of ABC on reproduction or fertility in male and female rodents has been seen at doses of up to 500 mg/kg per day. These doses produced exposures in rodents that were about eight times the exposures observed in humans who received the recommended dose. Exposures in this study were based on body surface area.

Teratogenicity/Adverse Pregnancy Outcomes

Rats treated with a dose of ABC 1,000 mg/kg during organogenesis showed signs of developmental toxicity (i.e., decreased fetal body weight and reduced crown-rump length) and had an increased incidence of fetal anasarca and skeletal malformations. This dose produced exposures in rats that were about 35 times those seen in humans who received the recommended dose; exposure was based on area under the curve. An increased number of resorptions and an increased incidence of stillbirths occurred among pregnant rats that received ABC 500 mg/kg once daily, beginning at embryo implantation and ending when the pups were weaned. Decreased fetal body weights were also observed, and the offspring had persistently low body weights throughout their lives. However, in rabbits, no evidence of drug-related developmental toxicity and no increase in fetal malformations were observed at doses of ABC up to 700 mg/kg. These doses produced exposures in rabbits that were about 8.5 times the exposures seen in humans who received the recommended dose.[1]

Placental and Breast Milk Passage

ABC crosses the placenta and is excreted into the breast milk of lactating rats.[1]

Human Studies in Pregnancy

Pharmacokinetics

In pregnant women, pharmacokinetic (PK) studies of ABC 300 mg twice daily[2] and ABC 600 mg once daily showed[3] that the PKs during pregnancy are equivalent to the PKs observed during the postpartum period. A population PK study (that analyzed 266 plasma samples from 150 pregnant women) found no effect of any co-variate (including age, body weight, pregnancy, or gestational age) on ABC PKs.[4] Thus, no dose adjustment for ABC is needed during pregnancy.

Placental and Breast Milk Passage

Placental transfer of ABC is high, with ratios of ABC concentration in cord blood to ABC concentration in maternal plasma at delivery of approximately 1.0.[2,5] In the Mma Bana study,[6] the median breast milk-to-plasma ratio for ABC was 0.85 in the 15 women tested at 1 month postpartum, and the drug was detected in the plasma of one out of nine breastfeeding infants whose mothers were receiving ABC.

Teratogenicity/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to ABC in humans have been monitored to be able to detect at least a 1.5-fold increase in risk of overall birth defects. No such

increase in birth defects has been observed with ABC. Among the cases of first-trimester ABC exposure that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.9% (36 infants out of 1,228 live births; 95% confidence interval, 2.1% to 4.0%).[7] This prevalence is similar to the prevalence of birth defects in the U.S. population, which is 2.72%, according to Centers for Disease Control and Prevention surveillance. First-trimester exposure to ABC was not associated with birth defects in the SMARTT study (adjusted odds ratio [aOR] 0.94, 0.53–1.65),[8] in the French Perinatal Study (aOR 1.01, 0.73–1.41),[9] or in a series of 897 births to women with HIV in Spain between 2000 and 2009 (aOR 0.99, 0.34–2.87).[10]

Pregnancy outcomes were similar between pregnant women who received an ABC/lamivudine (3TC) backbone (n = 252) and women who received a tenofovir disoproxil fumarate/emtricitabine backbone (n = 661) in the Italian National Program on Surveillance on Antiretroviral Treatment in Pregnancy. However, total cholesterol levels were higher in the group that received ABC.[11]

Ten percent of participants (711 pregnancies) received ABC plus 3TC in the EPPICC Study Group. The proportions of preterm deliveries and small-for-gestational-age infants that occurred among women who received ABC were similar to those seen among women who received other antiretroviral drugs.[12]

Other Safety Information

Serious hypersensitivity reactions (HSRs) have been associated with ABC therapy in nonpregnant adults, but these reactions have rarely been fatal; symptoms include fever, skin rash, fatigue, and gastrointestinal symptoms such as nausea, vomiting, diarrhea, or abdominal pain. ABC **should not be restarted** following an HSR, because more severe symptoms will occur within hours and may include life-threatening hypotension and death. Patients who test positive for HLA-B*5701 are at the highest risk of HSRs and should not receive ABC; HLA screening should be done before initiating ABC. Two meta-analyses have confirmed the association between this genotype and the HSR.[13,14]

After adjusting for birth cohort and other factors, the PHACS/SMARTT study (which followed participants for a median of 2.4 years) reported no increases in the likelihood of metabolic, cardiac, neurological, growth and development, or neurodevelopmental adverse events among infants whose mothers took ABC during pregnancy.[15]

Excerpt from Table 8

Note: When using FDC tablets, refer to other sections in Appendix B and Table 8 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
Abacavir (ABC) *Ziagen* (ABC/3TC) *Epzicom* (ABC/DTG/3TC) *Triumeq* (ABC/3TC/ZDV) *Trizivir* **Note:** Generic products are available for some formulations.	**ABC (Ziagen)[d]** *Tablet:* • 300 mg *Oral Solution:* • 20 mg/mL **ABC/3TC (Epzicom):[d]** • ABC 600 mg/3TC 300 mg tablet **ABC/DTG/3TC (Triumeq):** • ABC 600 mg/DTG 50 mg/3TC 300 mg tablet **ABC/3TC/ZDV (Trizivir):[d]** • ABC 300 mg/3TC 150 mg/ZDV 300 mg tablet	**Standard Adult Doses** *ABC (Ziagen):* • ABC 300 mg twice daily or ABC 600 mg once daily, without regard to food *ABC/3TC (Epzicom):* • One tablet once daily without regard to food *ABC/DTG/3TC (Triumeq):* • One tablet daily without regard to food *ABC/3TC/ZDV (Trizivir):* • One tablet twice daily without regard to food **Pregnancy** *PKs in Pregnancy:* • PKs not significantly altered in pregnancy. *Dosing in Pregnancy:* • No change in dose indicated. For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, ZDV, DTG).	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). HSRs occur in approximately 5% to 8% of nonpregnant individuals. A small percentage of reactions are fatal, and these fatal reactions are usually associated with re-challenge. Rate of reactions during pregnancy is unknown. Testing for HLA-B*5701 identifies patients at risk of reactions, and a patient's status **should be documented as negative** before initiating ABC. Patients should be educated regarding symptoms of HSR.

[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 10).

[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

[d] Generic formulation available.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; DTG = dolutegravir; FDC = fixed-dose combination; HSR = hypersensitivity reaction; PK = pharmacokinetic; ZDV = zidovudine

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