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Dolutegravir

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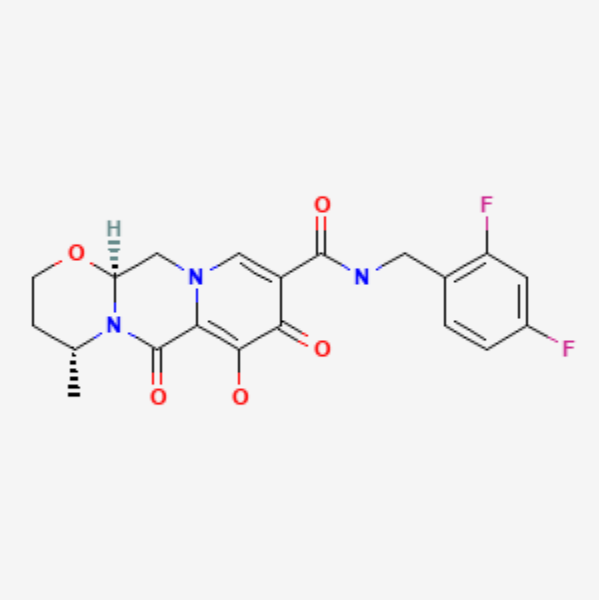
CASRN: 1051375-16-6



Drug Levels and Effects

Summary of Use during Lactation

Dolutegravir is detectable in maternal milk in low amounts. It appears that elimination by newborn infants is prolonged and the drug has been detected in infant plasma during breastfeeding. Dolutegravir has been used safely in HIV-positive mothers during breastfeeding and is recommended as a first-line drug during breastfeeding. Achieving and maintaining viral suppression with antiretroviral therapy decreases breastfeeding transmission risk to less than 1%, but not zero. Individuals with HIV who are on antiretroviral therapy with a sustained undetectable viral load and who choose to breastfeed should be supported in this decision. If a viral load is not suppressed, banked pasteurized donor milk or formula is recommended.[1,2]

Drug Levels

Maternal Levels. An HIV-positive mother took a combination tablet containing dolutegravir 50 mg, abacavir sulfate 600 mg and lamivudine 300 mg (Triumeq) once daily. Her breastmilk dolutegravir concentrations were measured periodically over a 10-month period and averaged about 100 mcg/L at 11 hours after the dose. The authors estimated a daily infant dosage of 15 mcg/kg of dolutegravir.[3]

Two HIV-positive women taking dolutegravir (dose not stated, but presumably 50 mg daily) plus 2 unspecified nonnucleoside reverse transcriptase inhibitors donated two milk samples each. At 2 weeks postpartum, steady-state breastmilk dolutegravir levels in one woman were 154.2 mcg/L at 4 hours after the dose and 40.9 mcg/L at 24 hours after a dose. In the other woman, steady-state breastmilk dolutegravir levels were 116.3 mcg/L at 3 hours after the dose and 17.7 mcg/L at 24 hours after a dose. At 2 and 9 days, respectively, after discontinuing the drug, breastmilk levels were undetectable (<10 mcg/L).[4]

Twenty-eight pregnant HIV-positive women were randomized to receive an antiretroviral regimen containing oral dolutegravir 50 mg once daily. Of these, 17 women underwent extensive postpartum sampling of breastmilk and maternal serum at a median of 10 days postpartum. Median dolutegravir peak concentration in milk was 84.6 mcg/L and minimum of 22.3 mcg/L. Only one woman had 14 mcg/L of dolutegravir in milk at 48 hours; all other milk samples at 48, 72 and 96 hours after drug discontinuation were negative for dolutegravir.[5] Data from this study were used to create a pharmacokinetic model of dolutegravir into milk. Using the model, the average concentration of dolutegravir in breastmilk over 24 hours was 0.05 mg/L (range 0.029-0.10 mg/L), corresponding to an absolute infant dose of 2.2 mcg/kg daily. This corresponds to a weight-adjusted infant dosage of 0.27% of the maternal dose.[6]

Six mothers taking dolutegravir 50 mg once daily provided milk samples at a median of 15 hours after a dose. The median drug concentration in milk was 107 mcg/L, which resulted in an estimated infant dosage of 20 mcg/kg daily and a relative infant dose of 1% of the maternal weight-adjusted dosage.[7]

Infant Levels. An HIV-positive mother took a combination tablet containing dolutegravir 50 mg, abacavir sulfate 600 mg and lamivudine 300 mg (Triumeq) once daily. Her infant had a plasma dolutegravir concentration of 100 mcg/L during the period of exclusive breastfeeding up to about 30 weeks postpartum. As supplemental feeding was introduced, the plasma concentrations dropped to about 30 mcg/L at 35 weeks, and to 0 with no breastfeeding after about 50 weeks postpartum.[3]

Two HIV-positive women taking dolutegravir (dose not stated, but presumably 50 mg daily) plus 2 unspecified nonnucleoside reverse transcriptase inhibitors breastfed their infants (extent not stated, but presumably exclusively). At 2 weeks postpartum, the plasma levels in one infant were 67.8 mcg/L and 75.5 mcg/L at 4 and 24 hours after the maternal dose, respectively. Two days after drug discontinuation, the infant had a plasma level of 58.6 mcg/L at a time when the maternal plasma level was 103.8 mcg/L. In the other infant, the plasma level was 16.3 mcg/L at 24 hours after the maternal dose.[4]

Seventeen women were receiving oral dolutegravir 50 mg daily as part of a study. Their breastfed infants had serum levels obtained at a median of 10 days postpartum. Their median dolutegravir peak serum concentration was 66.7 mcg/L and minimum was 60.9 mcg/L. After discontinuation of maternal dolutegravir, detectable concentrations were noted in 100%, 80% and 80% of breastfed infants at 48, 72 and 96 hours following final maternal dose, respectively. The ratio of paired maternal and infant serum concentrations was 0.03 at the peak and 0.08 at the trough.[5]

Twenty-one breastfed infants whose mothers were receiving dolutegravir postpartum had a total of 65 serum concentration measured postpartum. Infant serum concentrations were 4.9% of maternal plasma concentration in the first 24 hours after the final maternal dose, increasing to 11% of maternal plasma concentration when

measure over the 96 hours after the final maternal dose. The increase indicates a slower drug elimination in infants compared to their mothers.[6]

Two infants were breastfed by mothers taking dolutegravir 50 mg once daily, although the extent of breastfeeding was not sated. Infant serum concentrations taken at 1 month of age were 279 mcg/L at 15 hours after the dose in one infant and 100 mcg/L at 10 hours after the dose in the other.[7]

Effects in Breastfed Infants

An HIV-positive mother took a combination tablet containing dolutegravir 50 mg, abacavir sulfate 600 mg and lamivudine 300 mg (Triumeq) once daily. Her infant was exclusively breastfed for about 30 weeks and partially breastfed for about 20 weeks more. No obvious side effects were noted.[3]

In a study of African women with HIV infection received a dolutegravir-based regimen of 50 mg dolutegravir, 300 mg tenofovir disoproxil fumarate, and either 200 mg emtricitabine in South Africa or 300 mg lamivudine in Uganda during pregnancy and breastfeeding. This regimen was as safe for breastfed as an efavirenz-based regimen with the same other drugs.[8]

An open-label, controlled, multicenter phase 3 trial women who were confirmed HIV-positive were randomized to receive one of 3 regimens: dolutegravir, emtricitabine, and tenofovir alafenamide (n = 208); dolutegravir, emtricitabine, and tenofovir disoproxil fumarate (n = 202); or efavirenz, emtricitabine, and tenofovir disoproxil fumarate (n = 207). The regimens were started at 14 to 28 weeks of pregnancy and continued postpartum. Of the 617 liveborn infants, 99% were breastfeeding at time of last infant HIV test, which was as late as 50 weeks of age. The mean infant duration on the study was 47.6 weeks of age. Infants who had any clinical or laboratory adverse event of grade 3 or higher ranged from 25 to 31%, but was not statistically significant between groups. Dolutegravir-containing regimens resulted in lower rates of virological failure, HIV drug resistance, and infant mortality up to 50 weeks postpartum compared with efavirenz, emtricitabine, and tenofovir disoproxil fumarate.[9]

Effects on Lactation and Breastmilk

Relevant published information was not found as of the revision date.

Alternate Drugs to Consider

Raltegravir

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Substance Identification

Substance Name

Dolutegravir

CAS Registry Number

1051375-16-6

Drug Class

Breast Feeding

Lactation

Milk, Human

Anti-Infective Agents

Antiviral Agents

Anti-HIV Agents

Anti-Retroviral Agents

HIV Integrase Inhibitors