Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

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**Rilpivirine (Edurant, RPV)**

*(Last updated November 14, 2017; last reviewed November 14, 2017)*

Rilpivirine is classified as Food and Drug Administration Pregnancy Category B.

### Animal Studies

#### Carcinogenicity

Rilpivirine was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Rilpivirine was not carcinogenic in rats when administered at doses 3 times higher than exposure in humans at the recommended dose of 25 mg once daily. Hepatocellular neoplasms were observed in both male and female mice at doses 21 times that of human therapeutic exposure; the observed hepatocellular findings in mice may be rodent-specific.¹

#### Reproduction/Fertility

No effect on fertility was observed when rilpivirine was tested in rats at maternal doses up to 400 mg/kg/day, resulting in systemic drug exposure equivalent to 40 times the recommended human dose.¹

#### Teratogenicity/Adverse Pregnancy Outcomes

No evidence of embryonic or fetal toxicity or an effect on reproductive function was observed in rat and rabbit dams treated with rilpivirine during pregnancy and lactation. Exposures were 15 and 70 times higher in pregnancy and lactation, respectively, than exposure in humans at the recommended dose of 25 mg once daily.¹

### Placental and Breast Milk Passage

Studies in lactating rats and their offspring indicate that rilpivirine is present in rat milk.¹

### Human Studies in Pregnancy

#### Pharmacokinetics

A study presenting pharmacokinetic (PK) and safety data from 32 pregnant women with HIV found median rilpivirine area under the curve (AUC) and trough concentrations were reduced by about 20% to 30% in the second and third trimesters, compared with postpartum. Median trough rilpivirine concentrations were significantly lower at 14 visits where the women had detectable HIV-1 RNA (30 ng/mL) compared to 62 visits with undetectable HIV-1 RNA (63 ng/mL). Ninety percent of women had trough concentrations above the protein-adjusted EC₉₀ for rilpivirine. PK exposure was highly variable in this study.² Another study in 16 pregnant women with HIV found similarly decreased exposure by approximately 50% in the third trimester compared to postpartum.³ These authors recommended therapeutic drug monitoring in the third trimester, and also ensuring that rilpivirine doses are taken with meals. Cervicovaginal fluid rilpivirine concentrations were described in a study of 24 women taking rilpivirine daily during pregnancy and postpartum, which showed cervicovaginal rilpivirine steady-state concentrations similar to those seen in plasma in the same women. Rilpivirine cervicovaginal fluid AUC compared to plasma AUC was higher during pregnancy than postpartum.⁴

#### Placental and Breast Milk Passage

One of the PK and safety studies described above included rilpivirine delivery concentration data from 21 mother-infant pairs, with median (range) cord blood rilpivirine plasma concentration of 29.2 ng/mL (<10.0 to 101.5 ng/mL), maternal delivery plasma rilpivirine concentration of 55.2 ng/mL (<10.0 to 233.8 ng/mL) and cord blood/maternal plasma ratio of 0.55 (0.3 to 0.8).² Similarly, Colbers et al. found a median (range) cord blood-to-maternal plasma ratio of 0.5 (0.35–0.81) in 5 women.³ An *ex vivo* human cotyledon perfusion model also showed that rilpivirine crosses the placenta with fetal transfer rates ranging from 17% to 37%.⁵ No data exist on whether rilpivirine is excreted in breast milk in humans.

#### Teratogenicity/Adverse Pregnancy Outcomes

Among cases of first-trimester exposures to rilpivirine reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 0.5% (1 of 202 births; 95% CI, 0.0% to 2.7%) compared with a
total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.

Excerpt from Table 9

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation) Trade Name</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rilpivirine (RPV)</td>
<td>RPV (Edurant) Tablets: • 25 mg Complera: • RPV 25 mg plus TDF 300 mg plus FTC 200 mg tablet</td>
<td>Standard Adult Dose RPV (Edurant): • 25 mg once daily with food Complera: • 1 tablet once daily with food</td>
<td>Moderate to high placental transfer to fetus. No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).</td>
</tr>
<tr>
<td>Edurant</td>
<td>Odefsey: • RPV 25 mg plus TAF 25 mg plus FTC 200 mg tablet</td>
<td>Odefsey: • 1 tablet once daily with food</td>
<td></td>
</tr>
<tr>
<td>(RPV/TDF/FTC)</td>
<td>Complera</td>
<td>PK in Pregnancy: • RPV PK highly variable during pregnancy. RPV AUC and trough concentration reduced 20% to 50% in pregnancy compared with postpartum. While most pregnant women exceeded target exposure, those with detectable viral loads had lower RPV troughs. Dosing in Pregnancy: • While RPV plasma concentration is reduced during pregnancy, higher-than-standard doses have not been studied. Insufficient data are available to recommend a dosing change in pregnancy. With standard dosing, viral loads should be monitored more frequently.</td>
<td></td>
</tr>
<tr>
<td>(RPV/TAF/FTC)</td>
<td>Odefsey</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Individual ARV drug dosages may need to be adjusted in renal or hepatic insufficiency (Table 7).

Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio:

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

Key to Acronyms: AUC = area under the curve; FTC = emtricitabine; PK = pharmacokinetic; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

References