



## **Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**

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# Rilpivirine (RPV, Edurant) (Last updated April 27, 2017; last reviewed April 27, 2017)

For additional information see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf>

## Formulations

**Tablet:** 25 mg

### Fixed-Dose Combination Tablet:

- [Complera] Emtricitabine 200 mg plus rilpivirine 25 mg plus tenofovir disoproxil fumarate (TDF) 300 mg
- [Odefsey] Emtricitabine 200 mg plus rilpivirine 25 mg plus tenofovir alafenamide (TAF) 25 mg

## Dosing Recommendations

### Neonate/Infant Dose:

- Not approved for use in neonates/infants.

### Children Aged <12 Years:

- Not Food and Drug Administration-approved for use in children aged <12 years. For more information regarding consideration for use in children aged <12 years and weighing  $\geq 35$  kg, see the Pharmacokinetics section below.

### Adolescent (Weighing $\geq 35$ kg) and Adult Dose:

*Antiretroviral-Naive Patients with HIV RNA  $\leq 100,000$  copies/mL or Virologically-Suppressed (HIV RNA <50 copies/mL) Patients with No History of Virologic Failure or Resistance to Rilpivirine and Other Antiretroviral (ARV) Drugs and Currently on Their First or Second Regimen:*

- 25 mg once daily

### Combination Tablet

[Complera] Emtricitabine plus Rilpivirine plus TDF  
*Adolescent (Weighing  $\geq 35$  kg) and Adult Dose:*

- 1 tablet once daily in treatment-naive patients with baseline viral load <100,000 copies/mL or to replace a stable ARV regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) for at least 6 months with no history of treatment failure and have no known current or past substitutions associated with resistance to the individual components of Complera, and currently on their first or second regimen.

[Odefsey] Emtricitabine plus Rilpivirine plus TAF

*Adolescent (Weighing  $\geq 35$  kg) and Adult Dose:*

- 1 tablet once daily with a meal as initial therapy in those with no antiretroviral treatment history with HIV-1 RNA less than

## Selected Adverse Events

- Depression
- Insomnia
- Headache
- Rash (can be severe and include Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS])
- Hepatotoxicity
- Altered ACTH stimulation test of uncertain clinical significance

## Special Instructions

- Patients must be able to take rilpivirine with a meal of at least 500 calories on a regular schedule (a protein drink alone does not constitute a meal).
- Do not use rilpivirine with other non-nucleoside reverse transcriptase inhibitors.
- Do not use rilpivirine with proton pump inhibitors.
- Antacids should only be taken either at least 2 hours before or at least 4 hours after rilpivirine.
- Use rilpivirine with caution when co-administered with a drug with a known risk of *Torsades de Pointes* (see <https://www.crediblemeds.org/>).
- Do not start rilpivirine in patients with HIV RNA >100,000 copies/mL because of increased risk of virologic failure.

## Metabolism/Elimination

- Cytochrome P450 (CYP) 3A substrate
- Dosing in patients with hepatic impairment: No dose adjustment is necessary in patients

or equal to 100,000 copies per mL; or to replace a stable ART regimen in those who are virologically-suppressed (HIV-1 RNA <50 copies per mL) for at least 6 months with no history of treatment failure and have no known current or past substitutions associated with resistance to the individual components of Odefsey.

- with mild or moderate hepatic impairment.
- Rilpivirine decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but does not affect glomerular filtration.
- Dosing in patients with renal impairment: No dose adjustment is required in patients with mild or moderate renal impairment.
- Complera (fixed-dose combinations) should not be used in patients with CrCl <50 mL/min or in patients requiring dialysis.
- Use rilpivirine with caution in patients with severe renal impairment or end-stage renal disease. Increase monitoring for adverse effects because rilpivirine concentrations may be increased in patients with severe renal impairment or end-stage renal disease.
- When using Complera see the [tenofovir disoproxil fumarate section](#); when using Odefsey see the [tenofovir alafenamide section](#).

**Drug Interactions** (see also the [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#) and <http://www.hiv-druginteractions.org/>)

- *Metabolism*: Rilpivirine is a CYP 3A substrate and requires dosage adjustments when administered with CYP 3A-modulating medications.
- Before rilpivirine is administered, a patient's medication profile should be carefully reviewed for potential drug interactions.
- Co-administration of rilpivirine with drugs that increase gastric pH may decrease plasma concentrations of rilpivirine.
- Antacids should only be taken either at least 2 hours before or at least 4 hours after rilpivirine.
- H<sub>2</sub>-receptor antagonists should only be administered at least 12 hours before or at least 4 hours after rilpivirine.
- Do not use rilpivirine with proton pump inhibitors.
- Rifampin and rifabutin significantly reduce rilpivirine plasma concentrations; co-administration of rifampin with rilpivirine is contraindicated. For patients concomitantly receiving rifabutin, rilpivirine dose should be increased (doubled) to 50 mg once daily, taken with a meal.

### **Major Toxicities**

- *More common*: Insomnia, headache, and rash
- *Less common (more severe)*: Depression or mood changes, suicidal ideation.
- In adult studies, 7.3% of patients treated with rilpivirine showed a change in adrenal function identified by an abnormal 250-microgram ACTH stimulation test (peak cortisol level <18.1 micrograms/dL). In adolescent studies, 6/30 (20%) developed this abnormality.<sup>1</sup> The clinical significance of these results is unknown.

### **Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see [http://iasusa.org/sites/default/files/tam/october\\_november\\_2015.pdf#page=10](http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10)) and the Stanford University HIV Drug

Resistance Database offers a discussion of each mutation (see <http://hivdb.stanford.edu/DR/>).

## Pediatric Use

### Approval

With the viral load and antiretroviral (ARV) resistance restrictions noted above, rilpivirine in combination with other antiretroviral agents,<sup>1</sup> the combination tablet rilpivirine/emtricitabine/tenofovir disoproxil fumarate (Complera)<sup>2</sup> and the combination tablet rilpivirine/emtricitabine/tenofovir alafenamide (TAF) (Odefsey) are Food and Drug Administration-approved in persons aged  $\geq 12$  years and weighing  $>35$  kg.<sup>3</sup>

### Efficacy in Clinical Trials

A rilpivirine-containing regimen has been compared to an efavirenz-containing regimen in 2 large clinical trials in adults, ECHO and THRIVE. In both studies, rilpivirine was demonstrated to be non-inferior to efavirenz. Subjects with pretreatment HIV viral loads  $\geq 100,000$  copies/mL receiving rilpivirine had higher rates of virologic failure compared to those receiving efavirenz. These findings resulted in licensure for initial therapy with rilpivirine only in patients with HIV viral load  $\leq 100,000$  copies/mL.<sup>4-7</sup>

A study of rilpivirine, 25 mg daily in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs) in treatment-naïve adolescents aged 12 to 18 years, demonstrated that the regimen was well tolerated over 48 weeks. Among adolescents with baseline viral loads  $\leq 100,000$  copies/mL, 86% had a virologic response at 24 weeks and 79% at 48 weeks. Among adolescents with baseline viral loads  $>100,000$  copies/mL, 38% had a virologic response at 24 weeks and 50% at 48 weeks.<sup>8</sup>

Patients selected for rilpivirine use need to be able to take the drug on a regular schedule and with a full meal, which may limit its usefulness for some adolescents with an irregular schedule. Odefsey is a small pill, and can be useful for select patients who do not have any drug resistance mutations who might want to switch from a multi-pill regimen.

### Pharmacokinetics

The pharmacokinetics (PK), safety, and efficacy of rilpivirine in children aged  $<12$  years have not been established but are under study in patients aged 6 to  $<12$  years and weighing  $\geq 17$  kg ([ClinicalTrials.gov](http://ClinicalTrials.gov/identifier/NCT00799864) identifier NCT00799864). The Panel considers that rilpivirine may be appropriate in select children aged  $<12$  years as long as they weigh  $\geq 35$  kg; an expert in pediatric HIV infection should be consulted.

An international (India, Thailand, Uganda, and South Africa) Phase II trial, PAINT TMC278, investigated a 25-mg dose of rilpivirine in combination with 2 NRTIs in ARV-naïve adolescents aged 12 to  $<18$  years who weigh  $\geq 32$  kg and have a viral load  $\leq 100,000$  copies/mL.<sup>8</sup> In the dose-finding phase of the study, 11 youth aged  $>12$  to  $\leq 15$  years and 12 youth aged  $>15$  to  $\leq 18$  years underwent intensive PK evaluations after an observed dose of rilpivirine taken with a meal. PK were comparable to those in adults; results are listed in the table below.<sup>9</sup>

### Rilpivirine Pharmacokinetics in Adults and in Adolescents aged 12 to $<18$ Years<sup>1</sup>

Parameter	Adults	Adolescents Aged 12 to $<18$ years
Dose	25 mg once daily	25 mg once daily
Number studied	679	34
<b>AUC<sub>24h</sub> (ng•h/mL)</b>		
Mean $\pm$ Standard Deviation	2,235 $\pm$ 851	2,424 $\pm$ 1,024
Median (Range)	2,096 (198–7,307)	2,269 (417–5,166)
<b>C<sub>0h</sub> (ng/mL)</b>		
Mean $\pm$ Standard Deviation	79 $\pm$ 35	85 $\pm$ 40
Median (Range)	73 (2–288)	79 (7–202)

**Key to Acronyms:** AUC = area under the curve; C<sub>0</sub> = plasma concentration just prior to next dose;

In a PK study of youth aged 13 to 23 years receiving rilpivirine,<sup>10</sup> rilpivirine exposure was comparable to the results from PAINT in those receiving 25 mg rilpivirine without darunavir/ritonavir (DRV/r) and substantially higher in those receiving 25 mg rilpivirine with DRV/r (AUC = 6,740 ngxh/mL). No dose adjustments are currently recommended for adults when rilpivirine is used in DRV/r, where a similar 2- to 3-fold increase in rilpivirine exposure has been reported.<sup>1</sup>

### Toxicity

In the PAINT study the observed adverse events (AEs) were similar to those reported in adults (e.g., somnolence, nausea, vomiting, abdominal pain, dizziness, headache). The incidence of depressive disorders was 19.4% (7/36) compared to 9% in the Phase III trials in adults. The incidence of grades 3 and 4 depressive disorders was 5.6% (2/36).<sup>1</sup>

Six of 30 (20%) adolescents with a normal adrenocotrophic hormone stimulation test at baseline developed an abnormal test during the trial. There were no serious AEs, deaths, or treatment discontinuations attributed to adrenal insufficiency. The clinical significance of these results is not known but warrants further evaluation.<sup>1</sup>

## References

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