



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

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# Rilpivirine (RPV, Edurant) (Last updated April 16, 2019; last reviewed April 16, 2019)

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

## Formulations

**Tablets:** 25 mg

### Fixed-Dose Combination Tablets:

- [Complera] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil fumarate (TDF) 300 mg
- [Juluca] Dolutegravir 50 mg/rilpivirine 25 mg
- [Odefsey] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir alafenamide (TAF) 25 mg

## Dosing Recommendations

### Neonate and Infant Dose:

- Rilpivirine is not approved for use in neonates or infants.

### Children Aged <12 Years:

- Rilpivirine is not approved by the Food and Drug Administration for use in children aged <12 years (for more information, see the Pharmacokinetics section below).

### Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose:

- Rilpivirine 25 mg once daily **with a meal** in antiretroviral (ARV) treatment-naive patients who have HIV RNA ≤100,000 copies/mL or in patients who are virologically suppressed (HIV RNA <50 copies/mL) with no history of virologic failure or resistance to rilpivirine and other ARV drugs in the new regimen.

### [Complera] Emtricitabine/Rilpivirine/TDF

#### Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose:

- One tablet once daily **with a meal** in ARV treatment-naive patients with baseline viral loads ≤100,000 copies/mL. One tablet once daily can also be used to replace a stable ARV regimen in patients who are currently on their first or second regimen and who have been virologically suppressed (defined as HIV RNA <50 copies per mL) for ≥6 months with no history of treatment failure and no known current or past substitutions associated with resistance to the individual components of Complera.

### [Juluca] Dolutegravir/Rilpivirine

#### Adult Dose:

- One tablet once daily with a meal as a

## Selected Adverse Events

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

## Special Instructions

- **Do not start** rilpivirine in patients with HIV RNA >100,000 copies/mL due to increased risk of virologic failure.
- 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 at least 2 hours before or at least 4 hours after rilpivirine.
- **H2 receptor antagonists should only be administered at least 12 hours before or at least 4 hours after rilpivirine.**
- Use rilpivirine with caution when coadministering it with a drug that has a known risk of Torsades de Pointes (for more information, see [CredibleMeds](#)).
- When using fixed-dose combination (FDC) tablets, see other sections of the [Drug Appendix](#) for special instructions and

complete regimen to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies per mL) on a stable ARV regimen for ≥6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Juluca.

- Not approved for use in children or adolescents (see Simplification of Treatment section below).

**[Odefsey] Emtricitabine/Rilpivirine/TAF**  
**Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose:**

- One tablet once daily with a meal as initial therapy in ARV treatment-naïve patients with HIV RNA ≤100,000 copies per mL. One tablet once daily can also be used to replace a stable ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies per mL) for ≥6 months with no history of treatment failure and no known current or past substitutions associated with resistance to the individual components of Odefsey.

additional information about the individual components of the FDC.

### **Metabolism/Elimination**

- Cytochrome P450 (CYP) 3A substrate.

### **Rilpivirine Dosing in Patients with Hepatic Impairment:**

- No dose adjustment is necessary in patients with mild or moderate hepatic impairment.
- Rilpivirine decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but it does not affect glomerular filtration.

### **Rilpivirine Dosing in Patients with Renal Impairment:**

- No dose adjustment is necessary in patients with mild or moderate renal impairment.
- The FDC drugs Complera and Odefsey **should not be used** in patients with creatinine clearance <50 mL/min or <30 mL/min, respectively, or in patients who require dialysis.
- Use rilpivirine with caution in patients with severe renal impairment or end-stage renal disease. Rilpivirine concentrations may be increased in patients with severe renal impairment or end-stage renal disease, so monitoring for adverse events is especially important in these patients.
- When using Complera, see the [TDF section](#) of the guidelines; when using Odefsey, see the [TAF section](#).

### **Drug Interactions** (see also the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#))

- **Metabolism:** Rilpivirine is a cytochrome P450 (CYP) 3A substrate and requires dose adjustments when administered with CYP3A-modulating medications.
- A patient's medication profile should be carefully reviewed for potential drug interactions before rilpivirine is administered.
- Coadministering rilpivirine with drugs that increase gastric pH may decrease plasma concentrations of rilpivirine.
- Antacids should only be taken at least 2 hours before or at least 4 hours after rilpivirine.
- H2 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; coadministration of

rifampin with rilpivirine is **contraindicated**. For patients who are concomitantly receiving rifabutin, rilpivirine dose should be doubled to 50 mg once daily, taken with a meal.

- In a cohort of adolescent patients, rilpivirine exposure was two to three times greater when rilpivirine was administered in combination with darunavir/ritonavir (DRV/r) than when rilpivirine was administered alone.<sup>1</sup>

### **Major Toxicities**

- *More common:* Insomnia, headache, and rash.
- *Less common (more severe):* Depression or mood changes, suicidal ideation.
- In studies of adults, 7.3% of patients who were treated with rilpivirine showed a change in adrenal function characterized by an abnormal 250-microgram ACTH stimulation test (peak cortisol level <18.1 micrograms/dL). In a study of adolescents, six out of 30 patients (20%) developed this abnormality.<sup>2</sup> The clinical significance of these results is unknown.

### **Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a [list of updated resistance mutations](#) and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation.

**Transmitted drug resistance to second-generation non-nucleoside reverse transcriptase inhibitors (NNRTIs) may be present in infants and children who have recently received a diagnosis of HIV.**

### **Pediatric Use**

#### *Approval*

With the viral load and antiretroviral (ARV) resistance restrictions noted above, rilpivirine used in combination with other ARV agents,<sup>2</sup> the fixed-dose combination (FDC) tablet emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Complera),<sup>3</sup> and the FDC tablet emtricitabine/rilpivirine/tenofovir alafenamide (Odefsey) are all approved by the Food and Drug Administration (FDA) for use in persons aged  $\geq 12$  years and weighing  $\geq 35$  kg.<sup>4</sup> The FDC tablet of dolutegravir/rilpivirine (Juluca) is not approved for use in pediatric or adolescent patients at the time of this review.<sup>5</sup>

#### *Efficacy in Clinical Trials*

A rilpivirine-containing regimen has been compared to an efavirenz-containing regimen in two large clinical trials in adults, ECHO and THRIVE. In both studies, rilpivirine was demonstrated to be noninferior to efavirenz. Subjects with pretreatment HIV viral loads  $\geq 100,000$  copies/mL who received rilpivirine had higher rates of virologic failure than those who received efavirenz. These findings resulted in licensure for initial therapy with rilpivirine only in patients with HIV viral loads  $\leq 100,000$  copies/mL.<sup>6-9</sup>

A study of treatment-naïve adolescents aged 12 years to 18 years demonstrated that rilpivirine 25 mg, given once daily in combination with two nucleoside reverse transcriptase inhibitors (NRTIs), 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% had a virologic response at 48 weeks. Among adolescents with baseline viral loads  $> 100,000$  copies/mL, 38% had a virologic response at 24 weeks and 50% had a virologic response at 48 weeks.<sup>10</sup>

Rilpivirine may be used in carefully selected patients. Patients must be able to take rilpivirine on a regular schedule and with a full meal, which may limit its usefulness for some adolescents with irregular schedules. The FDC formulation Odefsey is a small pill and can be useful for select patients who **have difficulty swallowing pills but** who want to switch from a multipill regimen and who do not have any drug resistance mutations that are associated with the components of Odefsey.

A Spanish multicenter observational study enrolled 17 adolescents (aged <18 years of age) who acquired

HIV perinatally to receive emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Complera) as part of an off-label medication use program. At the time of enrollment, 12 patients were on a protease inhibitor-based regimen, four were on an NNRTI-based regimen, and one had not received antiretroviral therapy (ART). After a median follow-up of 90 weeks (for participants with undetectable viral loads at baseline) or 40 weeks (for participants with detectable viral loads at baseline), 86% and 89% of patients, respectively, achieved and maintained an undetectable viral load. None of the patients discontinued rilpivirine-based therapy because of adverse events (AEs); no skin rashes or central nervous system (CNS)-related events were observed. In addition, serum lipids improved and two adolescents with a history of insomnia and abnormal dreams while receiving efavirenz-based therapy did not report similar problems while receiving rilpivirine-based therapy.<sup>11</sup>

### 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 years to <12 years and weighing  $\geq 17$  kg (ClinicalTrials.gov identifier [NCT00799864](https://clinicaltrials.gov/ct2/show/study/NCT00799864)). The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) has agreed that rilpivirine may be appropriate for use in select children aged <12 years and weighing  $\geq 35$  kg. However, the Panel advises consulting an expert in pediatric HIV infection prior to using rilpivirine in this age group.

An international (India, Thailand, Uganda, and South Africa) Phase 2 trial, PAINT TMC278, investigated a 25-mg dose of rilpivirine given in combination with two NRTIs in ARV-naive adolescents aged 12 years to <18 years who weighed  $\geq 32$  kg and who had viral loads  $\leq 100,000$  copies/mL.<sup>10</sup> In the dose-finding phase of the study, 11 youth aged >12 years to  $\leq 15$  years and 12 youth aged >15 years to  $\leq 18$  years underwent intensive PK assessment after they took an observed dose of rilpivirine with a meal. PKs were comparable to those in adults; results are listed in the table below.<sup>12</sup>

**Table A. Rilpivirine Pharmacokinetics in Adults and in Adolescents Aged 12 Years to <18 Years**

Parameter	Adults	Adolescents Aged 12 Years to <18 Years
Dose	RPV 25 mg once daily	RPV 25 mg once daily
Number of Participants 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)

**Source:** Adapted from Rilpivirine [package insert]. Food and Drug Administration. 2018. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/202022s011lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202022s011lbl.pdf).<sup>2</sup>

**Key to Acronyms:** AUC<sub>24h</sub> = area under the curve after 24 hours; C<sub>0h</sub> = plasma concentration just prior to next dose; RPV = rilpivirine

In a PK study of youth aged 13 years to 23 years who received rilpivirine,<sup>1</sup> rilpivirine exposure was comparable to the results from PAINT in patients who received 25-mg doses of rilpivirine without DRV/r and substantially higher in those who received 25-mg doses of rilpivirine with DRV/r (area under the curve = 6,740 ng•h/mL). No dose adjustments are currently recommended for adults when rilpivirine is used with DRV/r, where a similar two-fold to three-fold increase in rilpivirine exposure has been reported.<sup>2</sup>

Rilpivirine has been reported to have fewer CNS AEs than efavirenz, and it has been promoted as a replacement ARV drug for some patients who experience CNS effects while receiving efavirenz. However, there has been concern that the prolonged half-life of efavirenz might result in residual drug levels that could



have an impact on rilpivirine levels. A Thai study evaluated 20 Thai adolescents 4 weeks after they switched from efavirenz to rilpivirine. The PK parameters of rilpivirine in this study population were comparable with those in previous pediatric (PAINT) and adult (ECHO/THRIVE) PK substudies. No virologic failure was detected at 12 or 24 weeks and no patients discontinued rilpivirine because of AEs.<sup>13</sup>

### *Simplification of Treatment*

Dolutegravir/rilpivirine (Juluca) is an FDC tablet that contains dolutegravir 50 mg and rilpivirine 25 mg. The recently reported results from two trials in adults (SWORD-1 and SWORD-2) support FDA approval of dolutegravir/rilpivirine as a complete regimen for treatment simplification or maintenance therapy in selected patients. The two identical SWORD trials enrolled 1,024 patients with suppressed viral replication who had been on stable ART for at least 6 months and had no history of treatment failure or evidence of resistance mutations that are associated with dolutegravir or rilpivirine. The participants were randomized to receive dolutegravir/rilpivirine or to continue their suppressive ARV regimen. After 48 weeks of treatment, 95% of patients in both arms maintained HIV RNA <50 copies/mL.<sup>14</sup> More AEs were reported and more AEs led to discontinuation in the dolutegravir/rilpivirine arm. In a subgroup of SWORD study patients whose original ARV regimen contained tenofovir disoproxil fumarate, small but statistically significant increases in hip and spine bone mineral density were observed.<sup>15</sup> Although dolutegravir/rilpivirine as Juluca is not approved for use in adolescents, the doses of both dolutegravir and rilpivirine in Juluca are approved for use in adolescents as single drugs. This product may be appropriate for certain adolescents; however, because the strategy of treatment simplification has not been evaluated in adolescents who may have difficulties adhering to therapy, the Panel **does not currently recommend** the use of Juluca for adolescents and children until more data are available.

### *Long-Acting, Injectable Rilpivirine*

Currently, a long-acting, injectable formulation of rilpivirine is under development as a treatment for adult patients (**to be given concurrently** with a cabotegravir long-acting injectable).<sup>16-18</sup> An IMPAACT study of the same regimen in adolescents is expected to begin enrolling participants in 2019.

### *Toxicity*

In the PAINT study, the observed 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% (seven of 36 participants) compared to 9% in the Phase 3 trials in adults. The incidence of Grades 3 and 4 depressive disorders was 5.6% (two of 36 participants).<sup>2</sup>

Six out of 30 adolescents (20%) with a normal adrenocotropic 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 abnormal adrenocotropic hormone stimulation tests is not known, but this finding warrants further evaluation.<sup>2</sup>

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