Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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### Darunavir (DRV, Prezista)  (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: [http://www.accessdata.fda.gov/scripts/cder/daf](http://www.accessdata.fda.gov/scripts/cder/daf)

#### Formulations

**Oral Suspension**: 100 mg/mL  
**Tablets**: 75 mg, 150 mg, 600 mg, 800 mg  
**Fixed-Dose Combination Tablets**:  
- [Prezcofax] Darunavir 800 mg/cobicistat 150 mg  
- [Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide (TAF) 10 mg

#### Dosing Recommendations

**Note**: Darunavir should not be used without a pharmacokinetic (PK) enhancer (boosting agent). Ritonavir may be used as the boosting agent in children and adults; cobicistat should only be used in adults.

**Neonate/Infant Dose**:  
- Darunavir is not approved for use in neonates/infants.

**Child Dose**

- **Aged <3 Years**:  
  - Do not use darunavir in children aged <3 years or weighing ≤10 kg. Seizures and death have been observed in infant rats who received darunavir, and these events have been attributed to immaturity of the blood-brain barrier and liver metabolic pathways.

- **Aged ≥3 Years to <12 Years**:  
  - Dosing recommendations in the table below are for children aged ≥3 years to <12 years and weighing ≥10 kg who are treatment-naive or treatment-experienced and with or without resistance testing results that demonstrate that they have at least one mutation that is associated with darunavir resistance.

#### Selected Adverse Events

- Skin rash, including Stevens-Johnson syndrome and erythema multiforme  
- Hepatotoxicity  
- Diarrhea, nausea  
- Headache  
- Hyperlipidemia, transaminase elevation, hyperglycemia  
- Fat maldistribution

#### Special Instructions

- Once-daily darunavir is not generally recommended for use in children aged <12 years or weighing <40 kg. Dosing estimates for these patients were based on limited data and there is limited clinical experience with this dosing schedule in this age group.

- Once-daily darunavir **should not be used** if any one of the following resistance-associated substitutions is present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, or L89V.

- Darunavir must be administered with food, which increases darunavir plasma concentrations by 30%.

- Darunavir contains a sulfonamide moiety. Use darunavir with caution in patients with known sulfonamide allergies.

- Pediatric dosing requires coadministration of tablets with different strengths to achieve the recommended doses for each weight band. It is important to provide careful instructions to caregivers when recommending a combination of different-strength tablets.

- Store darunavir tablets and oral suspension at room temperature (25°C or 77°F). Suspension
Boosting darunavir with cobicistat is currently not recommended in children aged <18 years; PKs, efficacy, and safety of darunavir/cobicistat is currently under investigation in children aged 12 years to 18 years.

### Child and Adolescent (Aged ≥12 Years and Weighing ≥30 to <40 kg) Dose for Treatment-Naive or Treatment-Experienced Patients With or Without at Least One Mutation Associated With Darunavir Resistance:
- Darunavir 450 mg (using a combination of tablets) plus ritonavir 100 mg, both twice daily with food

### Child and Adolescent (Aged ≥12 Years and Weighing ≥40 kg) and Adult Dose for Treatment-Naive or Treatment-Experienced Patients with No Mutations Associated With Darunavir Resistance:
- Darunavir 800 mg (using a tablet or combination of tablets) plus ritonavir 100 mg once daily with food

### Adult Dose for Treatment-Naive or Treatment-Experienced Patients with No Mutations Associated with Darunavir Resistance:
- Darunavir 800 mg (tablet) plus cobicistat 150 mg (tablet) or the coformulation Prezcobix once daily with food

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**Twice Daily Darunavir and Ritonavir Doses for Children Aged 3 Years to <12 Years and Weighing ≥10 kg**

<table>
<thead>
<tr>
<th>Weight</th>
<th>Dose (Twice Daily with Food)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 kg to &lt;11 kg</td>
<td>Darunavir 200 mg (2.0 mL) plus ritonavir 32 mg (0.4 mL)</td>
</tr>
<tr>
<td>11 kg to &lt;12 kg</td>
<td>Darunavir 220 mg (2.2 mL) plus ritonavir 32 mg (0.4 mL)</td>
</tr>
<tr>
<td>12 kg to &lt;13 kg</td>
<td>Darunavir 240 mg (2.4 mL) plus ritonavir 40 mg (0.5 mL)</td>
</tr>
<tr>
<td>13 kg to &lt;14 kg</td>
<td>Darunavir 260 mg (2.6 mL) plus ritonavir 40 mg (0.5 mL)</td>
</tr>
<tr>
<td>14 kg to &lt;15 kg</td>
<td>Darunavir 280 mg (2.8 mL) plus ritonavir 48 mg (0.6 mL)</td>
</tr>
<tr>
<td>15 kg to &lt;30 kg</td>
<td>Darunavir 375 mg (combination of tablets or 3.8 mL) plus ritonavir 48 mg (0.6 mL)</td>
</tr>
<tr>
<td>30 kg to &lt;40 kg</td>
<td>Darunavir 450 mg (combination of tablets or 4.6 mL) plus ritonavir (100 mg tablet or powder or 1.25 mL)</td>
</tr>
<tr>
<td>≥40 kg</td>
<td>Darunavir 600 mg (tablet or 6 mL) plus ritonavir 100 mg (tablet or 1.25 mL)</td>
</tr>
</tbody>
</table>

must be shaken well before dosing.

- When using fixed-dose combination (FDC) tablets, see other sections of the Drug Appendix for special instructions and additional information about the individual components of the FDC.

**Metabolism/Elimination**

- Cytochrome P450 3A4 substrate and inhibitor.

**Darunavir Dosing in Patients with Hepatic Impairment:**
- Darunavir is primarily metabolized by the liver. Caution should be used when administering darunavir to patients with hepatic impairment. Darunavir is not recommended in patients with severe hepatic impairment.

**Darunavir Dosing in Patients with Renal Impairment:**
- No dose adjustment is required in patients with moderate renal impairment (creatinine clearance 30–60 mL/min).
Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and HIV Drug Interaction Checker)

- **Metabolism**: Darunavir is primarily metabolized by cytochrome P450 (CYP) 3A4. Both ritonavir and cobicistat are inhibitors of CYP3A4, thereby increasing the plasma concentration of darunavir. Coadministration of darunavir plus ritonavir (DRV/r) or darunavir plus cobicistat (DRV/c) with drugs
that are highly dependent on CYP3A clearance creates potential for multiple drug-drug interactions and may be associated with serious and/or life-threatening events or suboptimal efficacy.

- Coadministration of several drugs, including protease inhibitors and rifampin, is contraindicated with DRV/r and DRV/c. A study involving adults with HIV suggested that etravirine may reduce serum darunavir concentrations by induction of CYP3A, which is more commonly expressed in individuals of African descent. Before administering darunavir (with or without ritonavir or cobicistat), a patient’s medication profile should be carefully reviewed for potential drug interactions.

  - When twice-daily DRV/r was used in combination with tenofovir disoproxil fumarate (TDF) in 13 patients with HIV aged 13 years to 16 years, both TDF and darunavir exposures were lower than those found in adults treated with the same combination. No dose adjustment is recommended when using DRV/r with TDF, but caution is advised and therapeutic drug monitoring may be useful. Data from the IMPAACT protocol P1058A indicate that coadministering once-daily DRV/r with once-daily or twice-daily etravirine in children, adolescents, and young adults aged 9 years to <24 years did not have a significant effect on darunavir plasma concentrations. When DRV/r was coadministered with etravirine twice daily in pediatric patients, target concentrations for both darunavir and etravirine were achieved. Darunavir pharmacokinetics (PKs) were not affected when darunavir was coadministered with rilpivirine in a study of adolescents and young adults. DRV/r coadministration increased rilpivirine exposure two-fold to three-fold; close monitoring for rilpivirine-related adverse events is advisable.

**Major Toxicities**

- **More common:** Diarrhea, nausea, vomiting, abdominal pain, headache, fatigue.
- **Less common:** Skin rash, including erythema multiforme and Stevens-Johnson syndrome, fever and elevated levels of hepatic transaminases, lipid abnormalities, and crystalluria.
- **Rare:** New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, and spontaneous bleeding in hemophiliacs. Hepatic dysfunction, particularly in patients with underlying risk factors such as hepatitis B or hepatitis C virus co-infection.

**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.

**Pediatric Use**

**Approval**

DRV/r is approved by the Food and Drug Administration (FDA) as a component of antiretroviral therapy (ART) in treatment-naive and treatment-experienced children aged ≥3 years.

**Efficacy in Clinical Trials**

In an international, multisite clinical trial (TMC114-TiDP29-C228) that enrolled treatment-experienced children aged 3 years to <6 years, 17 of 21 children (81%) who received DRV/r twice daily had viral loads <50 copies/mL at Week 48.

A randomized, open-label, multicenter pediatric trial that evaluated DRV/r twice daily among 80 treatment-experienced children aged 6 years to <18 years reported that 66% of patients had plasma HIV RNA <400 copies/mL and 51% had HIV RNA <50 copies/mL at Week 24.

Once-daily DRV/r has been investigated in a small study involving 12 treatment-experienced children aged 6 years to 12 years who had maintained HIV viral loads <50 copies/mL for at least 6 months. All but one child continued to have undetectable viral loads during a median of 11.6 months of follow-up (range: 0.5 months to 14.2 months). The remaining child had detectable viral load measurements between 20 copies/mL and...
200 copies/mL on three occasions during a 3-month period before again becoming undetectable, without a change in regimen.

**In one study, 12 participants aged 12 years to 17 years received DRV/r once daily.** After 48 weeks, all but one participant had viral loads <50 copies/mL.

**Pharmacokinetics and Dosing**

**Pharmacokinetics in Children Aged 3 Years to <6 Years**

Twenty-one children aged 3 years to <6 years and weighing 10 kg to <20 kg received twice-daily DRV/r oral suspension. These children had experienced virologic failure on their previous ART regimens and had fewer than three darunavir resistance mutations, confirmed by genotypic testing. The darunavir area under the curve (AUC0–12h), measured as a percent of the adult AUC value, was 128% overall: 140% in children weighing 10 kg to <15 kg and 122% in children weighing 15 kg to <20 kg.

**Pharmacokinetics in Children Aged >6 Years**

Initial pediatric PK evaluation of darunavir tablets and ritonavir oral solution or tablets was based on a Phase 2 randomized, open-label, multicenter study that enrolled 80 treatment-experienced children and adolescents aged 6 years to <18 years and weighing ≥20 kg. Part 1 of the trial used a weight-adjusted dose of darunavir 9 mg/kg to 15 mg/kg and ritonavir 1.5 mg/kg to 2.5 mg/kg twice daily, equivalent to the standard adult dose of DRV/r 600 mg/100 mg twice daily. This dose resulted in inadequate drug exposure in the pediatric population studied, with a 24-hour AUC (AUC24h) that was 81% of the AUC24h observed in adults and a pre-dose concentration (C0h) that was 91% of the C0h observed in adults. A pediatric dose that was 20% to 33% higher than the directly scaled adult dose was needed to achieve a drug exposure that was similar to that found in adults, and this was the dose selected for Part 2 of the study. The higher dose used for the safety and efficacy evaluation was darunavir 11 mg/kg to 19 mg/kg and ritonavir 1.5 mg/kg to 2.5 mg/kg twice daily. This resulted in a darunavir AUC24h of 123.3 mcg*h/mL (range 71.9–201.5 mcg*h/mL) and a C0h of 3,693 ng/mL (range 1,842–7,191 ng/mL), 102% and 114% of the respective PK values in adults. Doses were given twice daily and were stratified into body-weight bands of 20 kg to <30 kg and 30 kg to <40 kg. The current weight-band doses of twice-daily DRV/r for treatment-experienced pediatric patients weighing >20 kg to <40 kg were selected using the findings from the safety and efficacy portion of this study (see Table A).

A small study that involved 12 treatment-experienced children aged 6 years to 12 years examined the PKs and efficacy of DRV/r once daily administered in combination with abacavir and lamivudine. All participants had maintained HIV plasma viral loads <50 copies/mL for at least 6 months prior to beginning this regimen. The weight-based doses used for once-daily DRV/r were based on a prior modeling study: 600 mg/100 mg for patients weighing 15 kg to 30 kg, 675 mg/100 mg for patients weighing 30 kg to 40 kg, and 800 mg/100 mg for patients weighing >40 kg. The AUC0–24h geometric mean was below the study target of 80% of the value seen in adults (63.1 mg*h/L vs. 71.8 mg*h/L), but the trough values that were observed at 23.1 hours to 25.1 hours after the previous dose exceeded the trough plasma concentration recommended for treatment-experienced adults (0.55 mg/L). One child developed neuropsychiatric symptoms (anxiety and hallucinations) and was removed from study. This child did not have an excessive exposure to darunavir; the AUC0–24 was 47.8 mg*h/L.
Darunavir should not be used without a PK enhancer (boosting agent). Ritonavir may be used as the boosting agent in children and adults; cobicistat should only be used in adults. A study that enrolled 19 Thai children used the ritonavir 100-mg capsule twice daily as the boosting dose for twice-daily darunavir 375 mg (in children weighing 20 kg to <30 kg), 450 mg (in children weighing 30–40 kg), and 600 mg (in children weighing ≥40 kg). The darunavir exposures with ritonavir 100 mg twice daily were similar to those obtained in the studies with lower (<100 mg) doses of liquid ritonavir. The tolerability and PK data from this small study support the use of ritonavir 100 mg for boosting, using either the powder or tablet formulation, in children weighing ≥20 kg, particularly in instances where the lower-dose formulations are unavailable or a child does not tolerate the liquid ritonavir formulation. There are no data available on the safety and tolerability of using ritonavir 100 mg tablet or powder formulations in children weighing <20 kg.

Data on the dosing of DRV/c are only available for adult patients. Data on the use of a fixed-dose combination of DRV/c 800 mg/150 mg once daily showed bioavailability that was comparable to the bioavailability observed with the use of DRV/r 800 mg/100 mg once daily.

### Frequency of Administration

In February 2013, the FDA approved the use of once-daily darunavir for treatment-naive children and for treatment-experienced children without darunavir resistance-associated mutations (see Table B). Population PK modeling and simulation were used to develop recommendations for once-daily dosing in younger pediatric subjects aged 3 years to <12 years and weighing 10 kg to <40 kg. Currently, there is limited data on the efficacy of once-daily DRV/r dosing in treatment-naive or treatment-experienced children aged <6 years. Therefore, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) generally recommends dosing DRV/r twice daily in children aged ≥3 years to <12 years (see Once-Daily Administration in Children Aged <12 Years and Weighing <40 kg below). The Panel recommends that once-daily DRV/r be used only in treatment-naive and treatment-experienced adolescents weighing ≥40 kg who do not have mutations that are associated with darunavir resistance. If darunavir and ritonavir are used once daily in children aged <12 years, the Panel recommends conducting a PK evaluation.
of plasma concentrations of darunavir and closely monitoring viral load.

**Table B. Food and Drug Administration-Approved Dosing for Pediatric Patients Aged ≥3 Years and Weighing >10 kg who are Treatment-Naive or Treatment-Experienced with No Darunavir Resistance-Associated Mutations**

**Note:** The Panel generally recommends dosing darunavir plus ritonavir twice daily in children aged ≥3 years to <12 years.

<table>
<thead>
<tr>
<th>Weight</th>
<th>Dose (Once Daily with Food)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 kg to &lt;11 kg</td>
<td>DRV 350 mg (3.6 mL)(^a) plus RTV 64 mg (0.8 mL)(^c)</td>
</tr>
<tr>
<td>11 kg to &lt;12 kg</td>
<td>DRV 385 mg (4 mL)(^b) plus RTV 64 mg (0.8 mL)(^c)</td>
</tr>
<tr>
<td>12 kg to &lt;13 kg</td>
<td>DRV 420 mg (4.2 mL) plus RTV 80 mg (1 mL)(^c)</td>
</tr>
<tr>
<td>13 kg to &lt;14 kg</td>
<td>DRV 455 mg (4.6 mL)(^b) plus RTV 80 mg (1 mL)(^c)</td>
</tr>
<tr>
<td>14 kg to &lt;15 kg</td>
<td>DRV 490 mg (5 mL)(^b) plus RTV 80 mg (1 mL)(^c)</td>
</tr>
<tr>
<td>15 kg to &lt;30 kg</td>
<td>DRV 600 mg (tablet, combination of tablets, or 6 mL) plus RTV 100 mg (tablet, powder, or 1.25 mL)(^c)</td>
</tr>
<tr>
<td>30 kg to &lt;40 kg</td>
<td>DRV 675 mg (combination of tablets or 6.8 mL)(^b,d) plus RTV 100 mg (tablet or 1.25 mL)(^c)</td>
</tr>
<tr>
<td>≥40 kg</td>
<td>DRV 800 mg (tablet, combination of tablets, or 8 mL)(^d) plus RTV 100 mg (tablet or 1.25 mL)(^c)</td>
</tr>
</tbody>
</table>

\(^a\) The dose in children weighing 10 kg to 15 kg is DRV 35 mg/kg and RTV 7 mg/kg per dose, which is higher than the weight-adjusted dose in children with higher weights.

\(^b\) RTV 80 mg/mL oral solution.

\(^c\) The 350-mg, 385-mg, 455-mg, 490-mg, and 675-mg DRV doses are rounded for suspension-dose convenience.

\(^d\) The 6.8-mL and 8-mL DRV doses can be taken as two administrations (3.4 mL and 4 mL, respectively) once daily by refilling the oral dosing syringe supplied by the manufacturer, or as one administration once daily if a larger syringe is provided by a pharmacy or provider.

**Key to Acronyms:** DRV = darunavir; RTV = ritonavir

**Once-Daily Administration in Children Aged <12 Years and Weighing <40 kg**

During the TMC114-C228 trial, the researchers investigated once-daily dosing of darunavir for 2 weeks with PK evaluation in treatment-experienced children aged 3 years to <12 years as part of a substudy. After the conclusion of the substudy, the participants switched back to a twice-daily regimen.\(^{16,17}\) The DRV/r dose for once-daily use, which was based on PK simulation and which did not include a relative bioavailability factor, was darunavir 40 mg/kg coadministered with approximately 7 mg/kg of ritonavir for children weighing <15 kg, and DRV/r 600 mg/100 mg once daily for children weighing ≥15 kg.\(^{16,17}\) The PK data obtained from 10 children aged 3 years to 6 years in this substudy (see Table C) were included as part of the population PK modeling and simulation that was used to determine the FDA-approved dose for once-daily DRV/r in children aged 3 years to <12 years.

**In a small study in which DRV/r was administered once daily to 12 treatment-experienced children aged 6 years to 12 years,\(^9\)** the geometric mean AUC\(_{0-24\text{h}}\) achieved was below the study target of 80% of the value seen in adults (63.1 mg*h/L vs. 71.8 mg*h/L). Trough values exceeded the plasma concentration that is recommended for treatment-experienced patients (0.55 mg/L). Despite the FDA dosing guidelines, and because of the small set of data used for modeling and the limited amount of data on once-daily DRV/r in children aged <12 years, the Panel generally recommends dosing DRV/r twice daily in children aged ≥3 years to <12 years.
Once-Daily Administration in Adolescents Aged ≥12 and Weighing ≥40 kg

A substudy of once-daily dosing of DRV/r 800 mg/100 mg demonstrated that darunavir exposures in 12 treatment-naive adolescents (aged 12 years to 17 years and weighing ≥40 kg) were similar to those seen in adults treated with once-daily darunavir (see Table D). After 48 weeks, 83.3% of patients had viral loads <50 copies/mL and 91.7% had viral loads <400 copies/mL. Interestingly, no relationship was observed between darunavir AUC24h and C0h and virologic outcome (HIV RNA <50 copies/mL) in this study. Darunavir exposures were found to be similar to those observed in adults with once-daily dosing in another study in which a single dose of darunavir 800 mg with ritonavir 100-mg tablets was administered to 24 subjects with a median age of 19.5 years (range 14 years to 23 years). However, darunavir exposures were slightly below the lower target concentrations in adolescent patients aged 14 years to 17 years (N = 7) within the cohort, suggesting that higher doses may be needed in younger adolescents. A single case report involving a highly treatment-experienced adolescent patient suggests that using an increased darunavir dose with standard ritonavir boosting and employing TDM can lead to virologic suppression.

Table C. Pharmacokinetics of Once-Daily Darunavir in Children Aged 3 Years to 6 Years After 2 Weeks of Therapy with Ritonavir and Optimized Background Therapy

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Children Aged 3 Years to 6 Years (N = 10)17</th>
<th>Adults (N = 335)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRV AUC24h geometric mean, ng*h/mL (SD)</td>
<td>115 (40.6)</td>
<td>89.7 (27.0)</td>
</tr>
<tr>
<td>DRV C0h geometric mean, ng/mL (SD)</td>
<td>3.029 (1,715)</td>
<td>2,027 (1,168)</td>
</tr>
</tbody>
</table>

Key to Acronyms: AUC24h = 24-hour area under the curve; C0h = pre-dose concentration; DRV = darunavir; PK = pharmacokinetic; SD = standard deviation

Table D. Darunavir Pharmacokinetics with Once-Daily Administration in Adolescents Aged ≥12 Years and Adults Aged >18 Years

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>Dose of DRV/r</th>
<th>AUC24h² (mcg*h/mL) Median</th>
<th>C0h (ng/mL) Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescents Aged 12 Years to 17 Years (mean age 14.6 years)18</td>
<td>12</td>
<td>800 mg/100 mg</td>
<td>86.7</td>
<td>2,141</td>
</tr>
<tr>
<td>Adolescents and Adults Aged 14 Years to 23 Years (mean age 19.5 years)19</td>
<td>24</td>
<td>800 mg/100 mg</td>
<td>69.5</td>
<td>1,300</td>
</tr>
<tr>
<td>Adults Aged &gt;18 Years (Two studies)a</td>
<td>335/280</td>
<td>800 mg/100 mg</td>
<td>87.8–87.9</td>
<td>1,896–2,041</td>
</tr>
</tbody>
</table>

² Source: Darunavir [package insert]. Food and Drug Administration. 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021976s043,202895s017ibledt.pdf

Key to Acronyms: AUC24h = 24-hour area under the curve; C0h = pre-dose concentration; DRV/r = darunavir/ritonavir

The efficacy of once-daily darunavir has been established within a limited number of studies in small cohorts of adolescents that reported long-term data on virologic and immunologic outcomes.²⁰

References


