



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Darunavir (DRV, Prezista) (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

Oral suspension: 100 mg/mL

Tablets [Prezista]: 75 mg, 150 mg, 600 mg, and 800 mg

Fixed-Dose Combination Tablets

- [Prezcobix] Darunavir 800 mg plus Cobicistat 150 mg

Dosing Recommendations

Note: Darunavir should not be used without a pharmacokinetic (PK) enhancer (boosting agent): ritonavir (children and adults) or cobicistat (adults only).

Neonate/Infant Dose:

- Not approved for use in neonates/infants.

Pediatric Dose

Aged <3 years:

- **Do not use darunavir in children aged <3 years or weighing ≤10 kg** because of toxicity concerns based on seizures and death observed in infant rats and attributed to immaturity of the blood-brain barrier and liver metabolic pathways.

Aged ≥3 years:

- See table below for children aged ≥3 years who are antiretroviral **treatment-naïve and treatment-experienced** with or without one or more darunavir resistance-associated mutations.

Aged 3 to <12 Years and Weighing ≥10 kg

Weight (kg)	Dose (Twice daily with food) ^a
10 to <11 kg ^b	Darunavir 200 mg (2.0 mL) plus ritonavir 32 mg (0.4 mL)
11 to <12 kg ^b	Darunavir 220 mg (2.2 mL) plus ritonavir 32 mg (0.4 mL) ^c
12 to <13 kg ^b	Darunavir 240 mg (2.4 mL) plus ritonavir 40 mg (0.5 mL) ^c
13 to <14 kg ^b	Darunavir 260 mg (2.6 mL) plus ritonavir 40 mg (0.5 mL) ^c
14 to <15 kg	Darunavir 280 mg (2.8 mL) plus ritonavir 48 mg (0.6 mL) ^c
15 to <30 kg	Darunavir 375 mg (combination of tablets or 3.8 mL ^d) plus ritonavir 48 mg (0.6 mL ^d)
30 to <40 kg	Darunavir 450 mg (combination of tablets or 4.6 mL ^d) plus ritonavir 100 mg (tablet or 1.25 mL ^b)
≥40 kg	Darunavir 600 mg (tablet or 6 mL) plus ritonavir 100 mg (tablet or 1.25 mL)

Selected Adverse Events

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

Special Instructions

- In patients with one or more darunavir-associated mutations, darunavir should only be used twice daily. **Darunavir resistance-associated mutations are:** V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.
- Darunavir must be administered with food, which increases plasma concentrations by 30%.
- Darunavir contains a sulfonamide moiety. Use darunavir with caution in patients with known sulfonamide allergy.
- Pediatric dosing requires co-administration of tablets with different strengths to achieve the recommended doses depending on weight band. Careful instructions to caregivers when recommending a combination of different-strength tablets is very important.
- Store darunavir tablets and oral suspension at room temperature (25° C or 77° F). Suspension must be shaken well before dosing.

Metabolism/Elimination

- Cytochrome (CYP) P450 3A4 inhibitor and substrate.

Boosting darunavir with cobicistat is currently not recommended in children aged <18 years; PK, efficacy, and safety of darunavir/ cobicistat is currently under investigation in children aged 12 to 18 years.

Adolescent (Weighing ≥ 40 kg)^e and Adult Dose (Treatment-Naive or Treatment-Experienced with No Darunavir Resistance-Associated Mutations)

- Darunavir 800 mg (tablet or combination of tablets) plus ritonavir 100 mg **once daily**

Adult Dose (Treatment-Naive or Treatment-Experienced with No Darunavir Resistance-Associated Mutations):

- Darunavir 800 mg (tablet) plus cobicistat^f 150 mg (tablet) or coformulated as Prezcobix **once daily with food**

Adolescent (Weight ≥ 30 to <40 kg; Treatment-Experienced with at Least 1 Darunavir Resistance-Associated Mutation):

- Darunavir 450 mg (combination of tablets) plus ritonavir 100 mg both **twice daily with food**

Adolescent (Weight ≥ 40 kg) and Adult Dose (Treatment-Experienced With at least 1 Darunavir Resistance-Associated Mutation):

- Darunavir 600 mg plus ritonavir 100 mg, both **twice daily with food**
- The use of cobicistat **is not recommended** with darunavir 600 mg twice daily.

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.

Dosing in Patients with Renal Impairment:

- No dose adjustment is required in patients with moderate renal impairment (creatinine clearance [CrCl] 30–60 mL/min).

^a Once-daily dosing is Food and Drug Administration-approved but the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV does not recommend it for children (see text under Frequency of Administration).

^b Note that the dose in children weighing 10 to 15 kg is 20 mg/kg darunavir and 3 mg/kg ritonavir per kg body weight per dose, which is higher than the weight-adjusted dose in children with higher weight.

^c Ritonavir 80 g/mL oral solution

^d The 375-mg and 450-mg darunavir doses are rounded for suspension-dose convenience.

^e Some Panel members recommend once daily darunavir 675 mg (combination of tablets) plus ritonavir 100 mg once daily for adolescents with body weight ≥ 30 to <40 kg, especially those ≥ 12 years of age.

^f See [cobicistat section](#) for important information about toxicity, drug interactions, and monitoring patients who receive cobicistat.

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:** Darunavir is primarily metabolized by cytochrome P (CYP) 3A4. Both ritonavir and cobicistat are inhibitors of CYP3A4, thereby increasing the plasma concentration of darunavir. Potential exists for multiple drug interactions when either ritonavir or cobicistat is used with darunavir. Co-administration of darunavir/ritonavir or darunavir/cobicistat 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.
- Co-administration of several drugs, including **protease inhibitors and** rifampin, is contraindicated with ritonavir- or cobicistat-boosted darunavir. **Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions.**

Major Toxicities

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

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) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see <http://hivdb.stanford.edu/DR/>).

Pediatric Use

Approval

Darunavir co-administered with ritonavir is approved by the Food and Drug Administration (FDA) as a component of antiretroviral therapy (ART) in treatment-naïve and treatment-experienced children aged 3 years and older.

Efficacy in Clinical Trials

- Data from the randomized, open-label, multicenter pediatric trial, which evaluated darunavir with ritonavir twice daily among 80 treatment-experienced children aged 6 to <18 years, demonstrated that 66% of patients had week 24 plasma HIV RNA <400 copies/mL and 51% had HIV RNA <50 copies/mL.^{1,2}
- In an international, multisite clinical trial (TMC114-TiDP29-C228) involving treatment-experienced children aged 3 to <6 years, 81% of children (out of 21) had viral load <50 copies/mL at week 48.^{2,3}

Pharmacokinetics and Dosing

Pharmacokinetics in Children Aged 3 to <6 Years

Administration of twice-daily darunavir/ritonavir oral suspension in children aged 3 to <6 years and weighing 10 to <20 kg was conducted in 21 children who experienced failure of their previous ART regimen and had fewer than 3 darunavir resistance mutations on genotypic testing.¹⁻³ The darunavir area under the curve [AUC_(0-12h)], measured as a percent of the adult AUC value, was 128% overall: 140% in subjects weighing 10 to <15 kg and 122% in subjects weighing 15 to <20 kg.¹⁻³

Pharmacokinetics in Children Aged >6 Years

Using darunavir tablets and ritonavir liquid or tablets, initial pediatric pharmacokinetic (PK) evaluation was based upon a Phase II randomized, open-label, multicenter study that enrolled 80 treatment-experienced children and adolescents aged 6 to <18 years and weighing ≥ 20 kg.⁴ In Part I of the trial, a weight-adjusted dose of darunavir 9 to 15 mg/kg and ritonavir 1.5 to 2.5 mg/kg twice daily, equivalent to the standard adult dose of darunavir/ritonavir 600/100 mg twice daily, resulted in inadequate drug exposure in the pediatric population studied with 24-hour AUC (AUC_{24h}) of 81% and pre-dose concentration (C_{0h}) of 91% of the corresponding adult PK parameters. A pediatric dose 20% to 33% higher than the directly scaled adult dose was needed to achieve drug exposure similar to that found in adults and was the dose selected for Part II of the study. The higher dose used for the safety and efficacy evaluation was darunavir 11 to 19 mg/kg and ritonavir 1.5 to 2.5 mg/kg twice daily. This resulted in darunavir AUC_{24h} of 123.3 mcg*h/mL (range 71.9–201.5) and C_{0h} of 3,693 ng/mL (range 1,842–7,191), 102% and 114% of the respective PK values in adults. Doses were given twice daily and were stratified by body weight bands of 20 to <30 kg and 30 to <40 kg. Based on the findings in the safety and efficacy portion of the study, current weight-band doses of twice-daily darunavir/ritonavir for treatment-experienced pediatric patients with weight >20 to <40 kg were selected (see Table A).

Table A. Darunavir Pharmacokinetics with Twice-Daily Administration with Ritonavir and Optimized Backbone (Children Aged 3–18 Years and Adults Aged >18 Years)

Population	N	Dose of DRV/RTV	AUC _{12h} (mcg*h/mL) Median ^a	C _{0h} (ng/mL) Median ^a
10 to <15 kg ^a	13	20/3 mg/kg	66.0	3,533
10 to <15 kg ^a	4	25/3 mg/kg	116.0	8,522
15 to <20 kg ^a	11	20/3 mg/kg	54.2	3,387
15 to <20 kg ^a	14	25/3 mg/kg	68.6	4,365
Aged 6 to <12 years ^b	24	Weight bands ^b	56.4	3,354
Aged 12 to <18 years ^b	50	Weight bands ^b	66.4	4,059
Adults aged >18 years (3 studies) ^c	285/278/119	600/100 mg	54.7–61.7	3,197–3,539

^a Source: Food and Drug Administration. FDA pharmacokinetics review. 2011. Available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM287674.pdf>.

^b Weight band dosing was with darunavir/ritonavir at doses of 375/50 mg twice daily for body weight 20 to <30 kg, 450/60 mg twice daily for 30 to <40 kg, and 600/100 mg twice daily for ≥ 40 kg. Data from FDA pharmacokinetics review 2008. Available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm129567.pdf>.

^c Source: Darunavir [package insert]. Food and Drug Administration. 2016. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021976s043,202895s0171bledt.pdf.

Key to Acronyms: AUC = area under the curve; C_{0h} = pre-dose concentration; DRV = darunavir; RTV = ritonavir

Dosing

Pharmacokinetic Enhancers

Darunavir should not be used without a PK enhancer (boosting agent): ritonavir (children and adults) or cobicistat (adults only).

A study in 19 Thai children used ritonavir 100-mg capsule twice daily as the boosting dose with twice-daily darunavir doses of 375 mg (body weight 20 to <30 kg), 450 mg (body weight 30–40 kg), and 600 mg twice daily (body weight ≥ 40 kg).⁵ The darunavir exposures with 100-mg ritonavir twice daily were similar to those obtained in the studies with lower (<100 mg) liquid preparation-based ritonavir doses.^{4,5} The tolerability and PK data from this small study support the higher doses of ritonavir boosting with 100-mg capsule or tablet in children with body weight ≥ 20 kg, particularly when lower-dose formulations are unavailable or if a child

does not tolerate the liquid ritonavir formulation. Data are not available to evaluate the safety and tolerability of using ritonavir 100-mg tablet/capsule formulations in children who weigh less than 20 kg.

Data on dosing of cobicistat with darunavir are available in adult patients only.⁶ Data on a fixed-dose combination of 800/150 mg darunavir/cobicistat once daily showed comparable bioavailability to that obtained with 800/100 mg of darunavir/ritonavir once daily.⁷

Frequency of Administration

In February 2013, the FDA approved the use of once-daily darunavir for treatment-naïve children and for treatment-experienced children without darunavir resistance-associated mutations (see Table B). To derive once-daily pediatric dosing recommendations for younger pediatric subjects aged 3 to <12 years weighing 10 to <40 kg, population PK modeling and simulation were used.^{2,8} A dedicated pediatric trial evaluating once-daily darunavir with ritonavir dosing in children aged 6 to <12 years was not conducted. No efficacy data have been obtained regarding use of once-daily darunavir with ritonavir in treatment-naïve or treatment-experienced children aged <12 years. **Therefore, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV generally recommends dosing darunavir with ritonavir twice daily in children aged ≥3 years to <12 years** (see Once-Daily Dosing section). The Panel recommends that once-daily darunavir with ritonavir be used only in treatment-naïve and treatment-experienced adolescents **weighing ≥40 kg** who do not have darunavir resistance-associated mutations. If darunavir and ritonavir are used once daily in children aged <12 years, the Panel recommends conducting PK (measurement of plasma concentrations) evaluation (see [Therapeutic Drug Monitoring](#)) and close monitoring of viral load.

FDA approval was based on results from 2 small pediatric trials: TMC114-C230 evaluating once-daily dosing in treatment-naïve adolescents aged 12 to 18 years and weighing ≥40 kg (see below) and the TMC114-C228 sub-trial evaluating once-daily dosing in treatment-experienced children aged 3 to <6 years (see below).⁸⁻¹⁰

Table B. FDA-Approved Dosing for Pediatric Patients Aged ≥3 Years and Weighing >10 kg who are ART-Naïve or Treatment-Experienced with No Darunavir Resistance-Associated Mutations

Weight (kg)	Dose (Once daily with food)
10 to <11 kg ^a	DRV 350 mg (3.6 mL ^b) plus RTV 64 mg (0.8 mL ^c)
11 to <12 kg ^a	DRV 385 mg (4 mL ^b) plus RTV 64 mg (0.8 mL ^c)
12 to <13 kg ^a	DRV 420 mg (4.2 mL) plus RTV 80 mg (1 mL ^c)
13 to <14 kg ^a	DRV 455 mg (4.6 mL ^b) plus RTV 80 mg (1 mL ^c)
14 to <15 kg	DRV 490 mg (5 mL ^b) plus RTV 80 mg (1 mL ^c)
15 to <30 kg	DRV 600 mg (tablet or combination of tablets or 6 mL) plus RTV 100 mg (tablet or 1.25 mL ^c)
30 to <40 kg	DRV 675 mg (combination of tablets or 6.8 mL ^{b,d}) plus RTV 100 mg (tablet or 1.25 mL ^c)
≥40 kg	DRV 800 mg (tablet or combination of tablets or 8 mL ^d) plus RTV 100 mg (tablet or 1.25 mL ^c)

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

^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) with the included oral dosing syringe, or as one syringe when provided by pharmacy or medical office.

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

Key to Acronyms: DRV = darunavir; RTV = ritonavir

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

As part of the TMC114-C228 trial that evaluated twice-daily dosing in treatment-experienced children

aged 3 to <12 years, once-daily dosing of darunavir for 2 weeks with PK evaluation was conducted as a sub-study, after which the participants switched back to the twice-daily regimen.^{8,11} The darunavir/ritonavir dose for once-daily use in the trial, based on PK simulation (which did not include a relative bioavailability factor), was 40 mg/kg of darunavir co-administered with approximately 7 mg/kg of ritonavir once daily for children weighing <15 kg, and darunavir/ritonavir 600 mg/100 mg once daily for children weighing ≥15 kg.^{8,11} The PK data obtained from 10 children aged 3 to 6 years in this sub-study (Table C) were included as part of the population PK modeling and simulation, which proposed the FDA-approved dose for once-daily darunavir with ritonavir in children aged 3 to <12 years. **Despite the FDA dosing guidelines and because of the small set of data used for modeling and lack of efficacy data on once-daily darunavir with ritonavir in treatment-naïve or treatment-experienced children aged <12 years, the Panel generally recommends dosing darunavir with ritonavir twice daily in children aged ≥3 years to <12 years.**

Table C. Pharmacokinetics of Once-Daily Darunavir in Children Aged 3 to 6 Years After 2 Weeks of Therapy with Ritonavir and Optimized Backbone¹¹

PK Parameter	Once-Daily Darunavir Sub-Study (n = 10) 3–6 years	Adult Study (n = 335)
DRV AUC _{24h} geometric mean, ng*h/mL (SD)	115 (40.6)	89.7 (27.0)
DRV C _{0h} geometric mean, ng/mL (SD)	3,029 (1,715)	2,027 (1,168)

Key to Acronyms: AUC = area under the curve; C_{0h} = pre-dose concentration; DRV = darunavir; PK = pharmacokinetic; SD = standard deviation

Once-Daily Administration in Adolescents Aged ≥12 and Weighing ≥40 kg

A sub-study of once-daily dosing of darunavir 800 mg with ritonavir 100 mg in 12 treatment-naïve adolescents (aged 12–17 years and weighing ≥40 kg) demonstrated darunavir exposures similar to those seen in adults treated with once-daily darunavir (see Table D).⁹ In this study, the proportion of patients with viral load <50 copies/mL and <400 copies/mL at 48 weeks was 83.3% and 91.7%, respectively.¹⁰ Interestingly, no relationship was observed between darunavir AUC_{24h} and C_{0h} and virologic outcome (HIV RNA <50 copies/mL) in this study. Darunavir exposures were found to be similar to those 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 median age 19.5 years (14–23 years).¹² However, darunavir exposures were slightly below the lower target concentrations in adolescent patients aged 14 to 17 years (n = 7) within the cohort, suggesting the potential need for higher doses in younger adolescents. A single case report suggests the potential therapeutic benefit of virologic suppression using an increased darunavir dose with standard ritonavir booster following therapeutic drug monitoring (TDM) in a highly treatment-experienced adolescent patient.¹³

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

Population	N	Dose of DRV/RTV	AUC _{24h} ^a (mcg*h/mL) median	C _{0h} (ng/mL) median
Aged 12–17 years (mean 14.6) ⁹	12	800/100 mg	86.7	2,141
Aged 14–23 years (mean 19.5) ¹²	24	800/100 mg	69.5	1,300
Adults aged >18 years (2 studies) ^a	335/280	800/100 mg	87.8–87.9	1,896–2,041

^a Source: Darunavir [package insert]. Food and Drug Administration. 2016. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021976s043.202895s0171bledt.pdf.

Key to Acronyms: AUC_{24h} = 24-hour area under the curve; C_{0h} = pre-dose concentration; DRV = darunavir; RTV = 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.^{10,14}

Co-Administration with Other Antiretrovirals

Nucleotide Reverse Transcriptase Inhibitor

When darunavir/ritonavir twice daily was used in combination with tenofovir disoproxil fumarate (TDF) in 13 patients with HIV aged 13 to 16 years, both TDF and darunavir exposures were lower than those found in adults treated with the same combination.¹⁵ No dose adjustment is recommended for use of the combination of darunavir/ritonavir with either of these drugs, but caution is advised and therapeutic drug monitoring (TDM) may be potentially useful.

Non-Nucleoside Reverse Transcriptase Inhibitors

Recent data from the IMPAACT protocol P1058A report that the co-administration of once daily darunavir/ritonavir with etravirine administered once or twice daily to children, adolescents, and young adults aged 9 through <24 years did not have a significant effect on darunavir plasma exposure.¹⁶ When darunavir/ritonavir was co-administered with etravirine twice daily in pediatric patients, target concentrations for both darunavir and etravirine were achieved.¹⁷ When co-administered once daily, darunavir PKs have not been affected by co-administration of rilpivirine in adolescents and young adults.¹⁸ Darunavir/ritonavir co-administration increased rilpivirine exposure 2-to 3-fold, indicating that drug-related adverse effects should be closely monitored.

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