Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Darunavir (DRV, Prezista) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablets: 75 mg, 150 mg, 400 mg, and 600 mg

Oral suspension: 100 mg/mL

Dosing Recommendations

- DRV should not be used without ritonavir (RTV).

Neonate/infant dose:

- Not approved for use in neonates/infants.

Pediatric dose:

- *Age <3 years:*

Do not use DRV in children younger than age 3 years because of concerns related to seizures and death in infant rats associated with immaturity of the blood-brain barrier and liver metabolic pathways.

- *3 to <18 years of age and weighing ≥10 kg:*

Weight	Dose (both twice daily[a] with food)
10–<11 kg	DRV 200 mg (2 mL) + RTV 32 mg (0.4 ml[b])
11–<12 kg	DRV 220 mg (2.2 mL) + RTV 32 mg (0.4 ml[b])
12–<13 kg	DRV 240 mg (2.4 mL) + RTV 40 mg (0.5 ml[b])
13–<14 kg	DRV 260 mg (2.6 mL) + RTV 40 mg (0.5 ml[b])
14–<15 kg	DRV 280 mg (2.8 mL) + RTV 48 mg (0.6 ml[b])
15–<30 kg	DRV 375 mg (tablets or 3.75 mL oral suspension) + RTV 50 mg (0.6 ml[b])[c]
30–<40 kg	DRV 450 mg + RTV 60 mg (0.8 ml[b])[c]
≥40 kg	DRV 600 mg + RTV 100 mg

[a] *Do not use once-daily dosing in children aged <12 years or in any patient aged <18 years who is treatment-experienced (prior treatment failure). Once-daily dosing*

Selected Adverse Events

- Skin rash, including Stevens-Johnson syndrome and erythema multiforme
- Hepatotoxicity
- Diarrhea, nausea
- Headaches
- Possible increased bleeding in patients with hemophilia
- Hyperlipidemia, transaminase elevation, hyperglycemia
- Fat maldistribution

Special Instructions

- DRV must be administered with food, which increases area under the curve (AUC) and maximum plasma concentration (C_{max}) by 30%. Drug exposure is not significantly altered by the calorie and fat content of the meal.
- DRV contains a sulfonamide moiety. The potential for cross sensitivity between DRV and other drugs in the sulfonamide class is unknown. Use DRV with caution in patients with known sulfonamide allergy.
- Pediatric dosing requires administration of multiple 75-mg or 150-mg tablets to achieve the recommended doses of 375 mg or 450 mg depending on weight band. Careful instruction to caregivers is important. Pill burden may have a negative effect on adherence.
- Store DRV tablets and oral suspension at room temperature (25°C or 77°F). Oral suspension should be stored in the original container and shaken well before dosing.
- **Do not use once daily for:** children aged <12 years; for youth ages 12–18 years if treatment experienced (prior treatment failure); or in

(DRV 800 mg + RTV 100 mg can be used in treatment-naive pediatric patients aged 12–18 years and weighing ≥40 kg but is not FDA-approved for this population (see text). Note that the dose in children weighing 10–15 kg is 20 mg/kg body weight per dose, higher than the weight-adjusted dose in heavier (older) children.

[b] *RTV supplied as 80mg/mL oral solution.*

[c] *To enhance palatability—RTV 100 mg twice daily as the tablet formulation may be safely substituted for the liquid formulation for children ≥20 kg, even though the RTV dose is higher.*

Adolescent (aged ≥18 years)/adult dose (treatment-naive or antiretroviral-experienced with no DRV resistance associated mutations):

- DRV 800 mg + RTV 100 mg, both once daily with food.

Adolescent (aged ≥18 years)/adult dose (treatment experienced with at least one DRV resistance-associated mutation):

- DRV 600 mg + RTV 100 mg, both twice daily with food.

those aged ≥18 years if any of these DRV resistance associated mutations are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V

Metabolism

- Cytochrome P450 3A4 (CYP3A4) inhibitor and substrate.
- Dosing in patients with hepatic impairment: DRV is primarily metabolized by the liver. There are no data for dosing adult patients with varying degrees of hepatic impairment; caution should be used when administering DRV to such patients. DRV 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). There are no pharmacokinetic data in patients with severe renal impairment or end-stage renal disease.

Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- *Metabolism:* Darunavir is primarily metabolized by cytochrome P (CYP) 3A4. Ritonavir inhibits CYP3A4, thereby increasing the plasma concentration of darunavir. Potential exists for multiple drug interactions.
- 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.
- *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, or those with baseline elevation in transaminases).

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/DRV.html).

Pediatric Use: Darunavir boosted with ritonavir is Food and Drug Administration (FDA) approved for use twice daily in combination with ritonavir in children aged 3 years and older as part of combination antiretroviral therapy (cART), but is not FDA-approved for once-daily use in those younger than age 18 years.

Using darunavir tablets and ritonavir liquid or tablets, initial pediatric pharmacokinetic (PK) evaluation was based upon a randomized, open-label, multicenter study that enrolled 80 treatment-experienced pediatric participants ages 6 to <18 years and weighing ≥20 kg. The participants had a median age of 14 years (range 6–<18 years) and 71% were male, 54% were white, 30% black, 9% Hispanic, and 8% other race/ethnicity. Patients were stratified according to their weight and received darunavir/ritonavir plus background therapy consisting of at least two non-protease inhibitor antiretroviral (ARV) drugs.[1] The study was a two-part Phase II trial to evaluate the pharmacokinetics and tolerance of darunavir/ritonavir in children. In Part I, 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 area under the curve (AUC_{24h}) of 81% and pre-dose concentration (C_{0h}) of 91% of the corresponding adult pharmacokinetic 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 123,276ng*h/mL (range 71,850–201,520) and C_{0h} of 3,693 ng/mL (range 1,842–7,191), 102% and 114% of the respective PK values in adults. Patients were stratified by body weight: 20 to <30 kg and 30 to <40 kg. Doses were all given twice daily and were adjusted when patients changed weight categories. After the 2-week PK evaluation, all patients were allowed to switch to ritonavir 100-mg capsules, if desired, to avoid use of liquid oral ritonavir.

Based on the findings in the safety and efficacy portion of the study, weight-band doses of darunavir/ritonavir were chosen as follows: 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. As reported in the FDA clinical review (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm129560.pdf), for the 80 participants the Week 24 viral load was <400 copies/mL and <50 copies/mL in 66% and 51% respectively[2] (FDA snapshot analysis), and only 1 participant withdrew for an adverse event.

In this study, 27 of the 80 participants[1] switched from the ritonavir liquid solution to ritonavir 100-mg capsules, which are much easier to tolerate for children who can swallow pills. A separate study in 19 Thai children[3] used ritonavir 100 mg twice daily as the boosting ritonavir dose, with darunavir doses of 375 mg (body weight 20 to <30 kg), 450 mg (body weight 30 to 40 kg), and 600 mg twice daily (body weight ≥40 kg). The darunavir exposures of twice-daily darunavir doses boosted with 100 mg ritonavir twice daily showed values similar to those obtained with lower ritonavir doses. This regimen was well tolerated and adds further support to boosting with the easier to tolerate 100-mg capsule of ritonavir twice daily even in children as young as aged 6 years or weighing as little as 20 kg. Data are not available to evaluate the safety and tolerability of using ritonavir 100 mg in children who weigh less than 20 kg.

Darunavir oral suspension administered twice daily with ritonavir boosting has been studied in children aged 3 to <6 years and weighing 10 to <20 kg, reported in,[4] and in an FDA Clinical review.[2, 5] This trial was in N = 27 children ages 3 to <6 years who were failing their current antiretroviral therapy regimens and had fewer than 3 darunavir resistance-associated mutations on genotype testing. Participants were enrolled from Argentina, Brazil, India, Kenya, and South Africa. The initial dose for study was darunavir 20 mg/kg with ritonavir 3 mg/kg, both given twice daily, but higher-than-anticipated doses were required to achieve target drug exposures. Therefore, the dose used in these studies in this age and weight group

was increased to darunavir 25 mg/kg body weight combined with ritonavir 3 mg/kg body weight for children between 10 and 15 kg, and darunavir 375 mg plus ritonavir 50 mg for children 15 to <20 kg body weight. After dose adjustment, the darunavir AUC (0–12h), measured as a percent of the adult value, was 128% overall, 140% in the 10 to <15 kg weight band, and 122% in participants who weighed 15 to <20 kg (page 44 in http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM287674.pdf). At study week 24, 16 of 27 (59%) of these treatment-experienced subjects aged 3 to 6 years had viral load <50 copies/mL. This compares to a 75% virologic success rate in the 6- to 12-year-olds, and 39% in subjects aged 12 to 18 years (virologic success defined as viral load <50 copies/mL at 24 weeks) (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM287673.pdf). Diarrhea, vomiting, and rash were the most common side effects. The taste of the darunavir liquid is said to be better than the poor taste of the ritonavir needed for PK boosting, which is seen as a greater challenge to palatability.

When the study was completed, re-analysis of the PK data suggested that a dose of darunavir 20 mg/kg plus RTV 3 mg/kg body weight would be acceptable (table), and that re-analysis led to the final dosing recommendations found in the FDA product label.

Table. Darunavir Pharmacokinetic Results from Multiple Studies

Population	N	Dose of DRV/RTV and frequency	AUC_{24h}[a] (mcg*h/mL) median[b]	C_{0h} (ng/mL) median[b]
10–<15 kg[c]	13	20/3 mg/kg twice daily	122.0	3,533
10–<15 kg[c]	4	25/3 mg/kg twice daily	238.0	8,522
15–<20 kg[c]	11	20/3 mg/kg twice daily	108.4	3,387
15–<20 kg[c]	14	25/3 mg/kg twice daily	137.2	4,365
Aged 6–<12 years[d]	24	Weight bands,[d] twice daily	112.8	3,354
Aged 12–<18 years[d]	50	Weight bands,[d] twice daily	132.8	4,059
Adults aged >18 years (3 studies)[e]	285, 278, 119	600/100 mg twice daily	109.4–123.3	3,197–3,539
Once Daily				
Ages 12–17 (mean 14.6)[8]	12	800/100 once daily	87.9	2,196
Adults aged >18 years (2 studies)[e]	335, 280	800/100 once daily	87.8-87.9	1,896- 2,041

[a] For twice-daily (BID) dosing, AUC_{24h} is calculated as 2 times the AUC_{12h}.

[b] When more than two studies are included, a range of medians is listed.

[c] FDA pharmacokinetics review 2011 (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM287674.pdf)

[d] 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 (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm129567.pdf?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=darunavir&utm_content=10)

[e] Product label

When darunavir plus ritonavir twice daily was used in combination with etravirine in 40 HIV-infected patients aged 11 to 20 years, both darunavir and etravirine exposure were lower than that found in adults.[6] When darunavir plus ritonavir twice daily was used in combination with tenofovir in 13 HIV-infected patients aged 13 to 16 years, both tenofovir and darunavir exposures were lower than those found in adults treated with the same combination.[7]

Although darunavir is approved for once-daily dosing in ARV-naive adults, it should not be used once daily in children less than age 12 years because of more rapid clearance and absence of pediatric data. One small study (N = 12) of once-daily dosing (DRV 800 mg + RTV 100 mg) in treatment-naive adolescents aged 12 to 17 years and weighing ≥40 kg demonstrated good Week 24 virologic responses and darunavir exposures similar to those seen in adults treated with once-daily darunavir (see table above).[8]

References

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