Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Fosamprenavir (FPV, Lexiva) (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: 700 mg

Oral suspension: 50 mg/mL

Dosing Recommendations

Pediatric dose (aged >6 months–18 years):

- Unboosted FPV (without ritonavir [RTV]) is FDA-approved for antiretroviral (ARV)-naive children aged 2–5 years, but not recommended by the Panel because of low exposures (see text below).
- Boosted FPV (with RTV) is FDA-approved for ARV-naive infants at least 4 weeks of age and for treatment experienced infants at least 6 months of age; however, the Panel does not recommend use in infants younger than 6 months because of similarly low exposures (see text below). If used in infants as young as 4 weeks, it should only be administered to infants born at 38 weeks gestation or greater.

Aged ≥6 months–18 years:

Twice-Daily Dosage Regimens by Weight for Pediatric Patients at Least 6 Months of Age Using Lexiva Oral Suspension With Ritonavir

Weight	Dose FPV + RTV Both twice daily* with food
<11 kg	FPV 45 mg/kg + RTV 7 mg/kg
11 kg–<15 kg	FPV 30 mg/kg + RTV 3 mg/kg
15 kg–<20 kg	FPV 23 mg/kg + RTV 3 mg/kg
≥20 kg	FPV 18 mg/kg + RTV 3 mg/kg

*Not to exceed the adult dose of FPV 700 mg + RTV 100 mg twice daily.

Note: When administered with RTV, the adult regimen of 700 mg FPV tablets + 100 mg RTV, both given

Selected Adverse Events

- Diarrhea, nausea, vomiting
- Skin rash (FPV has a sulfonamide moiety. Stevens-Johnson syndrome and erythema multiforme have been reported.)
- Headache
- Hyperlipidemia, hyperglycemia
- Nephrolithiasis
- Transaminase elevation
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- FPV tablets with RTV should be taken with food. FPV tablets without RTV can be taken with or without food. Pediatric patients should take the suspension with food.
- Patients taking antacids or buffered formulations of didanosine (ddI) should take FPV at least 1 hour before or after antacid or ddI use.
- FPV contains a sulfonamide moiety. The potential for cross sensitivity between FPV and other drugs in the sulfonamide class is unknown. FPV should be used with caution in patients with sulfonamide allergy.
- Shake oral suspension well before use. Refrigeration is not required.

Metabolism

- The prodrug FPV is rapidly and almost completely hydrolyzed to amprenavir (APV) by cellular phosphatases in the gut as it is absorbed.

twice daily, can be used in patients weighing ≥39 kg. RTV pills can be used in patients weighing ≥33 kg.

Once-daily dosing is not recommended for any pediatric patient.

Adolescent (aged >18 years)/adult dose:

- Dosing regimen depends on whether the patient is ARV naive or ARV experienced.

ARV-naive patients:

- *Boosted with RTV, twice-daily regimen:* FPV 700 mg + RTV 100 mg, both twice daily.
- *Boosted with RTV, once-daily regimen:* FPV 1400 mg + RTV 100–200 mg, both once daily.

Protease inhibitor (PI)-experienced patients:

- FPV 700 mg + RTV 100 mg, both twice daily.

Once-daily administration of FPV + RTV is not recommended.

FPV in combination with efavirenz (EFV) (adults):

- Only FPV boosted with RTV should be used in combination with EFV.
- *Twice-daily regimen:* FPV 700 mg + RTV 100 mg, both twice daily + EFV 600 mg once daily.
- *PI-naive patients only, once-daily regimen:* FPV 1400 mg + RTV 300 mg + EFV 600 mg, all once daily.

FPV in combination with maraviroc (MVC) (adults):

- See MVC section for dosing of FPV with MVC.

- APV is a cytochrome P450 3A4 (CYP3A4) inhibitor, inducer, and substrate.
- Dosing in patients with hepatic impairment: Dosage adjustment is recommended. Please refer to the package insert.

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

- Fosamprenavir has the potential for multiple drug interactions.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with fosamprenavir.

Major Toxicities:

- *More common:* Vomiting, nausea, diarrhea, perioral paresthesias, headache, rash, and lipid abnormalities.
- *Less common (more severe):* Life-threatening rash, including Stevens-Johnson syndrome, in <1% of patients. Fat maldistribution, neutropenia, and elevated serum creatinine kinase levels.

- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, hemolytic anemia, elevation in serum transaminases, angioedema, and nephrolithiasis.
- *Pediatric specific:* In clinical trials of fosamprenavir, vomiting was more frequent in children than in adults (20%–60% vs. 10%–16%, respectively) as was neutropenia (15% vs. 3%, respectively).[1]

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/APV_FPV.html).

Pediatric Use: Fosamprenavir is Food and Drug Administration (FDA)-approved for use in children as young as age 4 weeks, but the Panel recommends use only for children aged 6 months or older. While unboosted fosamprenavir has been approved by the FDA for antiretroviral-naive children aged 2 to 5 years, the Panel does not recommend unboosted fosamprenavir for this or any other age group because of low exposures and because unboosted fosamprenavir may select for mutations associated with resistance to darunavir.[2]

Dosing recommendations for fosamprenavir are based on 3 pediatric studies that enrolled over 200 children aged 4 weeks to 18 years. In 2 open-label trials in both treatment-experienced and treatment-naive children from ages 2 to 18 years;[3, 4] fosamprenavir was well-tolerated and effective in suppressing viral load and increasing CD4 T lymphocyte count. However, data were insufficient to support a once-daily dosing regimen of ritonavir-boosted fosamprenavir in children; therefore, once-daily dosing is not recommended for pediatric patients.

In a study of infants, higher doses of both fosamprenavir and ritonavir were used in treatment-naive infants as young as age 4 weeks and in treatment-experienced infants as young as age 6 months.[1] Exposures in those younger than age 6 months were much lower than those achieved in older children and adults and comparable to those seen with unboosted fosamprenavir. Given these low exposures, limited data, large volumes, unpleasant taste, and the availability of alternatives for infants and young children, the panel does not recommend fosamprenavir use in infants younger than 6 months.

Population	Dose	AUC_{0-24} (mcg*hr/mL) except where noted	C_{min} (mcg/mL)
Infants <6 months	45 mg FPV/10 mg RTV per kg twice daily	26.6[a]	0.86
Children aged 2–<6 years	30 mg FPV per kg twice daily (no RTV)	22.3[a]	0.513
Children weighing <11 kg	45 mg FPV/7 mg RTV per kg twice daily	57.3	1.65
Children weighing 15–<20 kg	23 mg FPV/3 mg RTV per kg twice daily	121.0	3.56
Children weighing ≥20 kg	18 mg FPV/3 mg RTV per kg twice daily (max 700/100)	72.3–97.9	1.98–2.54
Adults	1400 mg FPV twice daily (no RTV)	33	0.35
Adults	1400 mg FPV/100–200 mg RTV once daily	66.4–69.4	0.86–1.45
Adults	700 mg FPV/100 mg RTV twice daily	79.2	2.12

[a] AUC_{0-12} (mcg*hr/mL)

Dose for those weighing 11 to <15 kg is based on population pharmacokinetic studies, therefore, area under the curve and C_{min} are not available.

References

1. Food and Drug Administration. Lexiva FDA Label. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021548s028,022116s012lbl.pdf.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. 2012.
3. Chadwick E, Borkowsky W, Fortuny C, et al. Safety and antiviral activity of fosamprenavir/ritonavir once daily regimens in HIV-infected pediatric subjects ages 2 to 18 years (48-week interim data, study apv20003). 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA.
4. Cunningham C, Freedman A, Read S, et al. Safety and antiviral activity of fosamprenavir-containing regmens in HIV-infected 2- to 18-year-old pediatric subjects (interim data, study apv29005). 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA.