



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

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# Fosamprenavir (FPV, Lexiva) (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

**Tablets:** 700 mg

**Oral Suspension:** 50 mg/mL

## Dosing Recommendations

### Pediatric Dose (Aged >6 Months to 18 Years):

- Unboosted fosamprenavir (without ritonavir) is Food and Drug Administration (FDA)-approved for antiretroviral (ARV)-naive children aged 2 to 5 years, but not recommended by The Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (the Panel) because of low exposures (see text below).
- Boosted fosamprenavir (with ritonavir) is FDA-approved for ARV-naive infants  $\geq 4$  weeks and for treatment-experienced infants  $\geq 6$  months; 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.

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

### Aged $\geq 6$ Months to 18 Years:

**Twice-Daily Dosage Regimens by Weight for Pediatric Patients  $\geq 6$  Months Using Lexiva Oral Suspension with Ritonavir**

Weight	Dose Fosamprenavir Plus Ritonavir Both twice daily <sup>a</sup> with food
<11 kg	fosamprenavir 45 mg/kg/dose plus ritonavir 7 mg/kg/dose
11 kg to <15 kg	fosamprenavir 30 mg/kg/dose plus ritonavir 3 mg/kg/dose
15 kg to <20 kg	fosamprenavir 23 mg/kg/dose plus ritonavir 3 mg/kg/dose
$\geq 20$ kg	fosamprenavir 18 mg/kg/dose plus ritonavir 3 mg/kg/dose

<sup>a</sup> Not to exceed the adult dose of fosamprenavir 700 mg plus ritonavir 100 mg twice daily.

## Selected Adverse Events

- Diarrhea, nausea, vomiting
- Skin rash (Fosamprenavir 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

- Fosamprenavir tablets with ritonavir should be taken with food. Children should take the suspension with food.
- Patients taking antacids or buffered formulations of didanosine should take fosamprenavir at least 1 hour before or after antacid or didanosine use.
- Fosamprenavir contains a sulfonamide moiety. The potential for cross sensitivity between fosamprenavir and other drugs in the sulfonamide class is unknown. Fosamprenavir should be used with caution in patients with sulfonamide allergy.
- Shake oral suspension well before use. Refrigeration is not required.

## Metabolism/Elimination

- The prodrug fosamprenavir is rapidly and almost completely hydrolyzed to amprenavir by cellular phosphatases in the gut as it is absorbed.
- Amprenavir is a cytochrome P450 3A4 (CYP3A4) inhibitor, inducer, and substrate.

**Note:** When administered with ritonavir, the adult regimen of 700 mg fosamprenavir tablets plus 100 mg ritonavir, both given twice daily, can be used in patients weighing  $\geq 39$  kg. Ritonavir tablets can be used in patients weighing  $\geq 33$  kg.

**Adolescent and Adult (Aged >18 Years) Dose:**

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

*ARV-Naive Patients*

Boosted with Ritonavir, Twice-Daily Regimen:

- Fosamprenavir 700 mg plus ritonavir 100 mg, both twice daily.

Boosted with Ritonavir, Once-Daily Regimen:

- Fosamprenavir 1400 mg plus ritonavir 100–200 mg, both once daily.

*Protease Inhibitor (PI)-Experienced Patients:*

- Fosamprenavir 700 mg plus ritonavir 100 mg, both twice daily.
- **Note:** Once-daily administration of fosamprenavir plus ritonavir is not recommended.

*Fosamprenavir in Combination with Efavirenz (Adult):*

- Only fosamprenavir boosted with ritonavir should be used in combination with efavirenz.

Twice-Daily Regimen:

- Fosamprenavir 700 mg plus ritonavir 100 mg, both twice daily plus efavirenz 600 mg once daily.

PI-Naive Patients Only, Once-Daily Regimen:

- Fosamprenavir 1400 mg plus ritonavir 300 mg plus efavirenz 600 mg, all once daily.

- 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](#) and <http://www.hiv-druginteractions.org/>)

- 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 paresthesia, 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 preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs, hemolytic anemia, elevation in serum transaminases, angioedema, and nephrolithiasis.
- *Pediatric specific:* Vomiting was more frequent in children than in adults in clinical trials of fosamprenavir with ritonavir (20% to 36% vs. 10%, respectively) and in trials of fosamprenavir without ritonavir (60% vs. 16%, respectively). Neutropenia was also more common in children across all the trials (15% vs. 3%, respectively).<sup>1</sup>

### ***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](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***

Fosamprenavir is Food and Drug Administration (FDA)-approved for use in children as young as age 4 weeks, but The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends use only in children aged 6 months or older. While unboosted fosamprenavir has been approved by the FDA for antiretroviral-naïve 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.<sup>2</sup>

#### ***Efficacy and Pharmacokinetics***

Dosing recommendations for fosamprenavir are based on three pediatric studies that enrolled over 200 children aged 4 weeks to 18 years. In two open-label trials in both treatment-experienced and treatment-naïve children aged 2 to 18 years,<sup>3,4</sup> 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.

#### ***Pharmacokinetics in Infants***

In a study of infants, higher doses of both fosamprenavir and ritonavir were used in treatment-naïve infants as young as 4 weeks and in treatment-experienced infants as young as 6 months.<sup>1,5</sup> Exposures in those younger than 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 dosing 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 <sub>0-24</sub> (mcg*hr/mL) Except Where Noted	C <sub>min</sub> (mcg/mL)
Infants <6 Months	45 mg fosamprenavir/10 mg ritonavir per kg twice daily	26.6 <sup>a</sup>	0.86
Children Aged 2 to <6 Years	30 mg fosamprenavir per kg twice daily (no ritonavir)	22.3 <sup>a</sup>	0.513
Children Weighing <11 kg	45 mg fosamprenavir/7 mg ritonavir per kg twice daily	57.3	1.65
Children Weighing 15 to <20 kg	23 mg fosamprenavir/3 mg ritonavir per kg twice daily	121.0	3.56
Children Weighing ≥20 kg	18 mg fosamprenavir/3 mg ritonavir per kg twice daily (maximum 700/100 mg)	72.3–97.9	1.98–2.54
Adults	1400 mg fosamprenavir twice daily (no ritonavir)	33	0.35
Adults	1400 mg fosamprenavir/100–200 mg ritonavir once daily	66.4–69.4	0.86–1.45
Adults	700 mg fosamprenavir/100 mg ritonavir twice daily	79.2	2.12

<sup>a</sup> AUC<sub>0-12</sub> (mcg\*hr/mL)

**Note:** Dose for those weighing 11 to <15 kg is based on population pharmacokinetic studies; therefore, area under the curve and C<sub>min</sub> are not available.

## References

1. Food and Drug Administration. LEXIVA (fosamprenavir calcium) package insert. Available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/021548s035,022116s019lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021548s035,022116s019lbl.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>. Accessed on November 25, 2014.
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. Fortuny C, Duiculescu D, Cheng K, et al. Pharmacokinetics and 48-week safety and antiviral activity of fosamprenavir-containing regimens in HIV-infected 2- to 18-year-old children. *Pediatr Infect Dis J*. 2014;33(1):50-56. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23811744>.
5. Cotton M, Cassim H, Pavia-Ruz N, et al. Pharmacokinetics, Safety and Antiviral Activity of Fosamprenavir/Ritonavir-containing Regimens in HIV-infected Children Aged 4 Weeks to 2 Years-48-week Study Data. *Pediatr Infect Dis J*. 2014;33(1):57-62. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23811743>.