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Fosamprenavir in Infants and Children with HIV-1 Infection

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On April 27, 2012, the Food and Drug Administration (FDA) announced the extension of approval for fosamprenavir to include patients 4 weeks of age and older with HIV-1 infection.¹ Fosamprenavir was approved by the FDA for use in adults on October 20, 2003 and has become a common part of highly active antiretroviral treatment (HAART) regimens.² Approval was extended to children over 6 years of age in October 2007. With the availability of new clinical research resulting in the extension of approval to infants and young children, fosamprenavir is now an option for more patients with HIV-1 infection.

Mechanism of Action

Fosamprenavir is a prodrug of amprenavir, a protease inhibitor. Amprenavir has demonstrated antiviral activity against HIV-1 in both acutely and chronically infected cells. It has exhibited synergistic effects when given in combination with nucleoside reverse transcriptase inhibitors (NRTIs) such as abacavir, didanosine, lamivudine, stavudine, tenofovir, and zidovudine, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as delavirdine and efavirenz, and two protease inhibitors, atazanavir and saquinavir. It has additive antiHIV-1 activity when given with the NNRTI nevirapine and the protease inhibitors indinavir, lopinavir, nelfinavir, and ritonavir, as well as enfuvirtide, a fusion inhibitor. Ritonavir is frequently administered with fosamprenavir to boost its effect.^{3,4}

Resistance to amprenavir has been documented in patients treated with fosamprenavir alone or in combination with ritonavir. Cross-resistance among the protease inhibitors has also been observed. In a premarketing clinical trial of adults receiving fosamprenavir and ritonavir, 54% demonstrated resistance to at least one protease inhibitor.^{3,4}

Pharmacokinetics

After oral administration, fosamprenavir is rapidly hydrolyzed to amprenavir in the intestinal epithelium, prior to reaching the systemic circulation. In adult clinical trials of

fosamprenavir given with ritonavir, the median time to peak amprenavir concentrations was 2.5 hrs, with a range of 1.5 to 4 hrs. Mean area under the concentration curve (AUC₂₄) was 66.4 to 79.2 mcg•hr per mL, with maximum amprenavir plasma concentrations (C_{max}) of 6.08 to 7.24 mcg/mL and minimum concentrations (C_{min}) of 0.86 to 2.12 mcg/mL. Administration of fosamprenavir alone produced an amprenavir AUC₁₂ of 33.0 mcg•hr per mL, with a C_{max} of 4.82 mcg/mL and a C_{min} of 0.36 mcg/mL.^{3,4}

Administration of fosamprenavir tablets with a high-fat meal in adults produced amprenavir serum concentrations similar to those produced when the drug was given to fasted subjects. Although food did not affect the absorption of the tablets, it resulted in a significant decrease in absorption of the oral suspension. The maximum amprenavir concentration (C_{max}) after a single 1,400 mg dose of the oral suspension given with a high-fat meal was 46% lower than that produced in fasted patients. There was also a 0.72 hr delay in the time to maximum concentration.^{3,4}

Amprenavir is 90% bound to plasma proteins, primarily alpha₁-acid glycoprotein. It is metabolized in the liver by cytochrome P450 3A4 (CYP3A4), forming two primary metabolites. Amprenavir may inhibit or induce CYP3A4 activity. Only 1% of a dose is eliminated unchanged in the urine. The average elimination half-life of amprenavir in adults is 7.7 hours. Hepatic dysfunction produces significant increases in amprenavir concentrations. Fosamprenavir dosing should be adjusted based on the degree of hepatic impairment.^{3,4}

The pharmacokinetic profile of fosamprenavir was studied in 212 children enrolled in three premarketing clinical trials conducted by the manufacturer. An inverse relationship between amprenavir clearance and patient weight was noted in these trials. When clearance was adjusted for weight, it was found to be higher in children younger than 4 years of age than in those who were older.³

In nine protease inhibitor-naïve patients younger than 6 months of age who were enrolled in a trial of fosamprenavir 45 mg twice daily plus ritonavir 10 mg/kg twice daily, the AUC_{12} was 26.6 mcg•hr per mL, with a C_{max} of 6.25 mcg/mL and a C_{min} of 0.86 mcg/mL. Weight-based fosamprenavir and ritonavir dosing, as described in the Dosing Recommendations section, produced amprenavir AUC_{24} values of 57.3 to 121 mcg•hr per mL, with a C_{max} of 5.03 to 9.54 mcg/mL and a C_{min} of 1.65 to 3.56 mcg/mL. The highest mean values were reported in the patient group weighing between 15 and 20 kg.³

Clinical Studies

In 2010, Palladino and colleagues published the first account of fosamprenavir use in children with HIV-1 infection.⁵ The authors reviewed their experience in 20 patients between 2 and 13 years of age. Six children were therapy-naïve. Only one patient received fosamprenavir alone; the rest received a ritonavir-boosted regimen. Additional therapy typically included lamivudine and abacavir. The median time of follow-up was 180 weeks. Eighteen (90%) of the patients achieved HIV-RNA levels below the limit of detection. Median increase from baseline CD4+ count was 217 cells/mm³ in the therapy-naïve patients and 251 cells/mm³ in the therapy-experienced patients. One patient developed a severe rash requiring discontinuation and another discontinued therapy after the emergence of resistance.

Three pediatric clinical trials have been conducted by the manufacturer.³ In the APV29005 trial, twice-daily fosamprenavir, with or without ritonavir, was studied in 109 children between 2 and 18 years of age. Twenty children, including 18 therapy-naïve and 2 therapy-experienced patients, received fosamprenavir twice daily for 24 weeks. At completion, the primary outcome, HIV-1 RNA < 400 copies/mL, had been achieved in 13 (65%) of the patients. The median increase from baseline in CD4+ count was 350 cells/mm³. Another 89 patients, 49 protease inhibitor-naïve and 40 protease inhibitor-experienced, received fosamprenavir with ritonavir twice daily. At week 24, 35 (71%) of the protease inhibitor-naïve and 22 (55%) of the protease inhibitor-experienced patients had achieved an HIV-1 RNA < 400 copies/mL. The median increase in CD4+ counts were 184 and 150 cells/mm³ in the two groups, respectively.

Fifty-four infants and children ranging from 4 weeks to 2 years of age were treated with fosamprenavir and ritonavir twice daily in the APV20002 trial. The patients in this trial were also receiving other antiretroviral therapies; 49 were protease inhibitor-naïve and 5 were

protease inhibitor-experienced. At 24 weeks, 72% of the patients had an HIV-RNA < 400 copies/mL. The median increase in CD4+ count was 400 cells/mm³ in the infants less than 6 months of age and 278 cells/mm³ in the patients between 6 months and 2 years of age. The third trial, APV20003, utilized once-daily fosamprenavir dosing with ritonavir, but the pharmacokinetic results from this study did not show adequate plasma amprenavir concentrations to support use of this regimen.³

Warnings and Precautions

Use of fosamprenavir can result in severe hypersensitivity reactions and was associated with the development of Stevens-Johnson syndrome in one patient during premarketing clinical trials. It should be discontinued in any patient with a severe rash or a rash associated with other systemic symptoms. Fosamprenavir should be used with caution in patients with a known sulfonamide allergy. Although fosamprenavir contains a sulfonamide moiety, the incidence of rash in clinical trials has not been significantly different between patients with a history of sulfonamide allergy and those without.^{3,4}

Elevations in serum transaminases have been reported in patients with underlying hepatitis B or C who are treated with fosamprenavir. New onset diabetes mellitus and hyperglycemia, fat redistribution, elevations in serum cholesterol and triglyceride levels, and nephrolithiasis have all been reported after initiation of fosamprenavir, although no causal relationships have been established.^{3,4}

Immune reconstitution syndrome has been reported in patients receiving combination antiretroviral therapy. As a result, patients beginning therapy with fosamprenavir should be monitored for an inflammatory response to residual opportunistic infections. These may include *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jirovecii* pneumonia, or *Mycobacterium tuberculosis*. Patients should also be monitored for the development of autoimmune disorders, including Guillain-Barré syndrome.^{3,4}

Adverse Effects

As in adults, the most frequently reported adverse effects with fosamprenavir in pediatric clinical trials included nausea and vomiting, headache, diarrhea, and rash. The incidence of vomiting in the children enrolled in the APV20002, APV20003, and APV29005 trials was 20-60%, significantly higher than the 10-16% incidence reported in adults. Grade 3 or 4 neutropenia (neutrophils < 750 cells per mm³)

was observed in 15% of children enrolled in clinical trials, compared to 3% of adults.^{3,4}

Drug Interactions

There are a large number of clinically significant drug interactions with fosamprenavir (Tables 1 and 2).^{3,4} Among the drugs known to interact with fosamprenavir, the manufacturer considers several to be contraindicated (Table 1). Grapefruit juice should also be avoided, as it may inhibit amprenavir metabolism leading to elevated plasma amprenavir concentrations. More detailed information on fosamprenavir is available in the prescribing information at www.lexiva.com (accessed 6/16/12).

Table 1. Contraindicated Fosamprenavir Drug Combinations^a

Drug or Drug Class	Effect
Alfuzosin	Hypotension
Cisapride	Arrhythmias
Delavirdine	Loss of virologic response
Dihydroergotamine, Ergotamine	Acute ergot toxicity
Flecainide	Inc concentrations leading to arrhythmias if used with ritonavir
Lovastatin	Myopathy
Midazolam	Inc sedation, respiratory depression
Pimozide	Arrhythmias
Propafenone	Inc concentrations leading to arrhythmias if used with ritonavir
Rifampin	Loss of virologic response
Sildenafil (for PAH)	Inc concentrations of sildenafil leading to toxicity
Simvastatin	Myopathy
St. John's wort	Loss of virologic response
Triazolam	Inc sedation, respiratory depression

^a Inc, increased; PAH, pulmonary arterial hypertension

Table 2. Potentially Significant Fosamprenavir Drug Interactions^a

Drug or Class	Effect or Recommendation
Antiarrhythmics (amiodarone, bepridil, dronedarone, lidocaine, quinidine)	Inc concentrations may lead to life-threatening arrhythmias
Anticonvulsants	Carbamazepine, phenobarbital, and phenytoin may reduce amprenavir concentrations. Fosamprenavir may lower phenytoin concentrations.
Azole antifungals	Inc concentrations of ketoconazole or itraconazole
Atorvastatin	May lower amprenavir concentrations
Benzodiazepines	Reduction of benzodiazepine dose may be needed
Bosentan	Reduced bosentan doses may be necessary
Calcium channel blockers	Close monitoring is recommended
Colchicine	Fosamprenavir dose reduction is necessary
Dexamethasone	May lower amprenavir concentrations

Efavirenz	Additional ritonavir is recommended when given with fosamprenavir/ritonavir once daily. No change is needed with twice daily dosing.
Fluticasone	Reduced cortisol concentrations; use not recommended
H ₂ blockers	May lower amprenavir concentrations
Immunosuppressants: cyclosporine, tacrolimus, rapamycin	Therapeutic drug monitoring recommended
Macrolide antibiotics (clarithromycin and erythromycin)	Use with caution, may lower amprenavir concentrations
Nevirapine	Not recommended with fosamprenavir alone. No dose change required when dosing fosamprenavir/ritonavir twice daily.
Oral contraceptives	Use not recommended; may lead to loss of virologic response
PDE5 inhibitors: sildenafil, tadalafil, vardenafil used intermittently	Inc PDE5 inhibitor concentrations; reduced doses of these drugs are recommended
Paroxetine	Fosamprenavir/ritonavir may lower paroxetine concentrations
Rifabutin	Reduce rifabutin dose by at least 50% and monitor for neutropenia
Salmeterol	Inc salmeterol concentrations; use not recommended
Trazodone	Inc trazodone concentrations
Tricyclic antidepressants	Therapeutic drug monitoring recommended
Warfarin	Altered warfarin concentrations; close INR monitoring recommended

^a Inc, increased

Availability and Cost

Fosamprenavir (Lexiva[®]) is produced by GlaxoSmithKline and marketed by ViiV Healthcare.³ It is available as 700 mg tablets, in bottles of 60 tablets, and a 50 mg/mL grape-bubblegum-peppermint-flavored oral suspension. The average wholesale price of the 60 tablet bottle is approximately \$860, while a 225 mL (7.5 ounce) bottle of the oral suspension is approximately \$130. The manufacturer offers a patient savings card program that provides a \$100 discount per month on any of their prescription drug products. Information on applying for the card is available at <http://www.mysupportcard.com/index.html> (accessed 6/16/12).

Dosing Recommendations

In therapy-naïve adults, fosamprenavir should be initiated at a dose of 1,400 mg twice daily. If boosted with 100 or 200 mg ritonavir, the dose can be given once daily. A regimen of fosamprenavir 700 mg twice daily plus ritonavir

100 mg twice daily is recommended for adults who have previously received other protease inhibitors and may also be used in therapy-naïve adult patients.^{3,4}

A twice-daily, weight-based dosing regimen is recommended for infants and children. Fosamprenavir should only be initiated in infants who were born at a minimum of 38 weeks gestation and are at least 4 weeks of age. In protease inhibitor-naïve patients, fosamprenavir may be initiated at dose of 30 mg/kg given twice daily. Ritonavir-boosted fosamprenavir may be used in protease inhibitor-naïve patients 4 weeks of age and older or protease inhibitor-experienced patients 6 months of age and older (Table 3). Once-daily dosing is not recommended for pediatric patients.^{3,4}

Table 3. Pediatric Fosamprenavir Dosing

Weight	Dose (given twice daily)
< 11 kg	45 mg/kg with ritonavir 7 mg/kg
11-14.9 kg	30 mg/kg with ritonavir 3 mg/kg
15-19.9 kg	23 mg/kg with ritonavir 3 mg/kg
≥ 20 kg	18 mg/kg with ritonavir 3 mg/kg, to a max of 700 mg fosamprenavir and 100 mg ritonavir

There is no information on dosing fosamprenavir in infants or children with hepatic impairment. In adults, a dose reduction to 700 mg twice daily, with or without ritonavir 100 mg once daily, is recommended for those with mild impairment (Child-Pugh scores of 5-6). In patients with moderate hepatic impairment (Child-Pugh scores of 7-9), fosamprenavir should be reduced to 700 mg twice daily without ritonavir for therapy-naïve patients or 450 mg twice daily with 100 mg ritonavir once daily for therapy-naïve or therapy-experienced patients. In those with severe hepatic impairment (Child-Pugh scores of 10-15), the dose of fosamprenavir should be reduced to 350 mg twice daily alone in therapy-naïve patients or 300 mg twice daily with 100 mg ritonavir once daily in therapy-naïve or therapy-experienced patients.^{3,4}

Fosamprenavir tablets may be taken with or without food. In adults, the oral suspension should be taken without food, but in children it may be given with food to improve palatability. While the oral suspension may be stored at room temperature, refrigeration may improve the taste. If emesis occurs within the first 30 minutes after a fosamprenavir dose, it should be repeated.^{3,4}

Summary

Fosamprenavir has become a frequent part of HAART regimens in adults and older children with HIV-1 infection. The recent FDA approval

for use in infants as young as 4 weeks of age allows the benefits of this highly effective therapy to be extended to even the youngest patients. Additional research is still needed, however, to evaluate the long-term safety and efficacy of fosamprenavir in the pediatric population.

References

1. Food and Drug Administration. New pediatric Lexiva dosing regimen for patients from at least 4 weeks to less than 6 years of age. Available at: <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm302447.htm> (accessed 6/18/12).
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4. Porkoma J, Machala L, Rezacova P, et al. Current and novel inhibitors of HIV protease. *Viruses* 2009;1:1209-39.
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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their June meeting:

1. Indomethacin suppositories (Indocin[®]) were added to the Formulary for use in high-risk patients to prevent post-ERCP pancreatitis.
2. Rufinamide (Banzel[®]) was added for the treatment of seizures in children and adults with Lennox Gastaut Syndrome.
3. Pertuzumab (Perjeta[™]) was added to the Formulary for treatment of metastatic breast cancer, with restriction to Outpatient use.
4. The restriction on ferumoxytol (Feraheme[®]) was amended to include use in patients requiring rapid administration of iron in the inpatient setting.
5. The restriction on tranexamic acid was amended to include use in trauma patients treated under the Massive Transfusion Protocol.

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