Fosamprenavir

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Fosamprenavir (Lexiva) is a new formulation of the older protease inhibitor amprenavir (Agenerase). Like all protease inhibitors, fosamprenavir works by inhibiting the HIV protease enzyme, which HIV needs to replicate. Other approved drugs in this class include amprenavir, atazanavir, indinavir, Kaletra, nelfinavir, ritonavir and saquinavir.

Who should use it?

Fosamprenavir is approved for use in combination with other anti-HIV drugs in adults. When used as part of second or third line therapy, it may need to be "boosted" with a small amount of ritonavir.

What does the research show?

The Food and Drug Administration (FDA) approval of fosamprenavir was supported by the results of several studies. Two studies, called APV30001 and APV30002 compared fosamprenavir with the approved protease inhibitor (PI) nelfinavir (Viracept). In both studies everyone also received abacavir (Ziagen), 300mg twice a day and 3TC (Epivir), 150mg twice a day, and none had taken anti-HIV drugs before. The results of the studies were similar. APV30001 found that 66% of people receiving fosamprenavir achieved undetectable viral loads (<400) compared to 52% of those receiving nelfinavir. APV30002 found that 69% of people receiving fosamprenavir, 1,400mg once a day with low dose ritonavir (Norvir) 200mg once a day, achieved undetectable viral loads, compared to 68% of people taking nelfinavir.

APV30003 compared fosamprenavir boosted with a small amount of ritonavir to Kaletra (lopinavir/ritonavir) in people who had taken protease inhibitors before, and whose anti-HIV drug regimens were failing. After 48 weeks, 58% of people receiving fosamprenavir/ritonavir had undetectable viral loads, versus 61% of those receiving Kaletra. The study was not large enough to show whether fosamprenavir/ritonavir is equal to Kaletra in treating people who have previously used other protease inhibitors.

How to use it?

There are three different ways to take fosamprenavir and the decision on how to use it will largely have to do with whether or not you've used anti-HIV medications in the past and/or whether your HIV has developed resistance to other protease inhibitors.

- People who have never taken anti-HIV drugs, or whose HIV is not resistant to other protease inhibitors can take fosamprenavir with or without ritonavir boosting. Without boosting with ritonavir, the dose is two 700mg tablets, twice a day (total daily dose of 2,800mg).
- When boosting with ritonavir people can either take a twice daily regimen of one 700mg tablet along with 100mg of ritonavir (total daily dose of 1,400mg fosamprenavir, 200mg ritonavir), or
- A once daily regimen of two 700mg tablets along with 200mg of ritonavir (total daily dose of 1,400mg fosamprenavir, 200mg ritonavir).

The twice-daily ritonavir boosted regimen is recommended for people whose virus is resistant to other protease inhibitors.

What is ritonavir boosting?

A small amount of ritonavir is used to increase the amount of some drugs in the body and keep them in the body longer. There are a few advantages to this approach. First it can increase the strength and effectiveness of some drugs. It can also sometimes overcome drug and food interactions. Sometimes it reduces the number of pills a person needs to take, or how often they must take them. The disadvantage of this approach is that ritonavir interacts with many drugs, both prescription and over the counter. Special care should be taken when using ritonavir.

People with impaired liver function may need to reduce the dose of fosamprenavir. No studies combining fosamprenavir with ritonavir in people who have impaired liver function have been conducted to date, though dose reductions may be necessary when using a boosted regimen as well.

What about side effects?

The most common reported side effects associated with fosamprenavir use include diarrhea, nausea, vomiting, headache and rash. Elevations in cholesterol and triglycerides are seen, as are changes in the amount and distribution of body fat—called lipodystrophy. In rare cases (<1%) a serious, potentially life-threatening rash called Stevens-Johnson Syndrome has occurred in people taking fosamprenavir.

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What about drug resistance?

HIV resistance to fosamprenavir is likely to be a concern, and thus the drug should be used in combination with other anti-HIV therapies. Resistance to a drug occurs when the virus changes or modifies itself such that it is no longer crippled in its replication cycle by the effects of a drug. Cross-resistance is when resistance to one drug also causes resistance to other drugs. Studies suggest that cross-resistance to other protease inhibitor drugs, in particular, is likely to be a problem with fosamprenavir.

Once a person has developed resistance to fosamprenavir, they are very likely not going to benefit as well from other approved protease inhibitors. It might be possible, however, to use boosted doses of these other therapies to overcome some of this resistance. It is unclear if ritonavir boosting of fosamprenavir will be able to overcome and control HIV resistant to other protease inhibitors.

HIV and the brain

Because HIV can infect brain cells, it's important to consider a drug's ability to reach the brain when putting together an anti-HIV regimen. It's probably wise to include at least one drug that has been shown to cross the blood-brain barrier to some useful degree as part of your regimen. These include AZT, d4T, abacavir, nevirapine, amprenavir, atazanavir and to a lesser degree indinavir and 3TC. Fosamprenavir has not been shown to cross the barrier to a significant degree, although it might be expected to since the older form of amprenavir does.

What about drug interactions

There are a number of drug interactions with fosamprenavir, including interactions with drugs commonly used among people living with HIV. People should work closely with their doctor or pharmacist to identify any potential drug interactions and make any necessary dose adjustments. For more information on drug interactions call Project Inform's hotline and ask for the publication, *Drug Interactions*.

Due to serious and potentially life-threatening drug interactions, fosamprenavir should not be taken with amiodarone, lidocaine (systemic), tricyclic antidepressants (e.g. amyltriptiline, doxapin), quinadine, ergot derivatives, antiarrhythmics (e.g. procainamide, amiodarone) rifampin, cisapride, lovastatin, simvistatin, pimozide, midazolam and triazolam.

What is known about this drug for women, people of color, children, and the elderly?

Fosamprenavir has not been studied in pregnant women and thus is generally discouraged for use in either pregnant or nursing women. It is not known if fosamprenavir is excreted in breast milk. Because HIV can be passed through breast milk, nursing is generally discouraged in areas where alternatives exist. Results from preliminary studies in animals do not suggest that there will be a problem with fosamprenavir use during pregnancy, but animal studies do not always predict safety in humans.

Fosamprenavir has not been well researched in children. Not enough people over the age of 65 were included in studies to provide special/unique information for the elderly to consider. Studies have been conducted to look at differences in how fosamprenavir is broken down, used and cleared (*pharmacokinetic* studies) in the bodies in black people and people who are not black. There appears to be no racial differences in the pharmacokinetics of fosamprenavir among black people compared to other people. Moreover, there do not appear to be differences in the way the drug is processed or cleared based on sex.

How do I get it?

Fosamprenavir is available by prescription at hospitals and pharmacies. Many states will likely cover fosamprenavir through their AIDS Drug Assistance Programs (ADAP). To find out if you're eligible for your state ADAP and if fosamprenavir is covered through your state's program, contact Project Inform at 1-800-822-7422. Information is also available from AIDS Treatment Data Network at 1-800-734-7104 or *www.atdn.org*. People who lack insurance, Medicaid, ADAP coverage or other ways to buy the drug might gain access to it through the company's Patient Assistance Program 1-866-728-4368.

Commentary

Fosamprenavir is a new version of the older protease inhibitor amprenavir. One of the main drawbacks to amprenavir is the number of pills it requires (8 pills, twice daily). Fosamprenavir only requires two to four pills a day, depending on whether or not it is

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boosted with ritonavir. This reduction in pill count could be beneficial to increase ease of use and thus increase people's ability to take the pills regularly as prescribed (adherence). Fosamprenavir needs to be taken regularly as prescribed, as part of a combination of anti-HIV drugs.

Important questions remain about how and when to use fosamprenavir. Studies suggest that it is an average strength protease inhibitor, with the possible benefit of once-a-day dosing (with ritonavir boosting) and no food restrictions. Fosamprenavir appears to have similar affects on body fats as nearly all other protease inhibitors. People who are taking amprenavir successfully can probably safely switch to fosamprenavir, and gain the benefit of fewer pills. People who have developed HIV resistance to amprenavir are unlikely to benefit from this newer version. As an option for first line therapy, fosamprenavir offers the benefit of few pills and no food restrictions.

It retains the problems with blood fats seen with most other PIs. It remains unclear whether people with resistance to other protease inhibitors would benefit from taking fosamprenavir.

The Bottom Line

Benefits:

- Fewer pills than its sister drug, amprenavir.
- Can be taken with or without food.
- When boosted with ritonavir, once daily dosing is possible (especially for those who have not developed resistance to other protease inhibitors).

Concerns:

- People with HIV resistant to amprenavir will not likely benefit from fosamprenavir.
- Resistance and cross-resistance with other protease inhibitors.
- Numerous possible interactions with medications commonly used by people with HIV.
- Most frequent side effects include: diarrhea, nausea, vomiting, headache and rash.

How to get it:

- GlaxoSmithKline Patient Assistance Program, call 1-866-728-4368.
- Available through hospitals and pharmacies.
- Available through some state AIDS Drug Assistance Programs.

The Basic Message

- *Learn about HIV testing options and choose one that fits your needs! Be sure your privacy is protected!*
- *If you're positive, don't panic. If you make your health a priority, chances are you will be reasonably healthy for many years.*
- *Learn about your healthcare options and local support services.*
- *Get a complete physical and blood tests for CD4+ cell count & HIV level. Repeat quarterly and watch for trends. Women should get GYN exams and Pap tests every six months, more often if abnormal.*
- *Work with a doctor to develop a long-term strategy for managing HIV disease.*
- *If the CD4+ cell count is below 350 or falling rapidly, consider starting anti-HIV therapy. Test at least twice before taking action.*
- *If anti-HIV therapy fails to reduce your HIV level below the "limit of detection" or below 5,000 copies within 3–6 months, consider a different or more aggressive therapy.*
- *If the CD4+ count trend stays below 300, consider treatment for preventing PCP. If it stays below 200, start treatment for preventing PCP (if you haven't already done so) and reconsider anti-HIV therapy if not on one. Learn about drug interactions and preventive treatments for opportunistic infections.*
- *If you started preventive therapies and your CD4+ cell count rises in response to anti-HIV therapy, ask your doctor whether it might be safe to stop certain preventive therapies.*
- *If your CD4+ cell count stays below 75, consider more frequent blood work—perhaps even monthly. Consider therapies for preventing MAC/MAI and CMV.*
- *Regularly seek support for your personal, spiritual and emotional needs. It takes more than medicines to keep you well.*

HELPFUL READING FROM PROJECT INFORM

Day One; Building a Doctor/Patient Relationship; Making Decisions; and Anti-HIV Therapy Strategies