

Fosamprenavir calcium

Brand Name: Lexiva



Drug Description

Fosamprenavir is the calcium phosphate ester prodrug of amprenavir, an inhibitor of HIV protease. Fosamprenavir calcium is a single stereoisomer with the (3S)(1S,2R) configuration. [1]

HIV/AIDS-Related Uses

Fosamprenavir was approved by the FDA on October 20, 2003, for the treatment of HIV-1 infection in combination with other antiretrovirals. [2] [3]

Pharmacology

Fosamprenavir is rapidly and almost completely hydrolyzed to amprenavir and inorganic phosphate by cellular phosphatases in the gut epithelium as it is absorbed. Amprenavir binds to the active site of HIV-1 protease and prevents the processing of viral Gag and Gag-Pol polyprotein precursors, resulting in the formation of immature, noninfectious viral particles. [4]

Fosamprenavir has been studied in both healthy adult volunteers and HIV infected patients; no substantial differences in steady-state amprenavir concentrations were observed between the two populations. The time to peak amprenavir concentration (T_{max}) after administration of a single dose of fosamprenavir occurred between 1.5 and 4 hours (median 2.5 hours). The absolute oral bioavailability of amprenavir after administration of fosamprenavir has not been established. [5]

When administered twice daily with ritonavir, the median maximum plasma concentration (C_{max}) was 6.08 microg/ml, the median T_{max} was 1.5 hours, and the median area under the concentration-time curve (AUC) was 79.2 microg x hour/ml. [6]

In vitro, amprenavir is approximately 90% bound to plasma proteins, with concentration-dependent binding observed over the concentration range of 1 to 10 microg/ml. The partitioning of amprenavir into erythrocytes is low but increases as amprenavir

concentrations increase, reflecting the higher amount of unbound drug at higher concentrations. [7]

Amprenavir is metabolized in the liver by the cytochrome P450 3A4 (CYP3A4) enzyme system. The two major metabolites result from the oxidation of the tetrahydrofuran and aniline moieties. The plasma elimination half-life of amprenavir is approximately 7.7 hours. Excretion of unchanged amprenavir in the urine and feces is minimal. [8]

Fosamprenavir is in FDA Pregnancy Category C. [9] It is not known whether amprenavir crosses the human placenta; however, it does cross the placenta in rats. [10] There are no adequate and well-controlled studies to date using the drug in pregnant women. Fosamprenavir should be used during pregnancy only when clearly needed. An Antiretroviral Pregnancy Registry has been established to monitor the outcomes of pregnant women exposed to antiretroviral agents, including fosamprenavir. Physicians may register patients by calling 1-800-258-4263 or at the following website: <http://www.APRegistry.com>. It is not known whether amprenavir is distributed into human milk; however, it is distributed into milk in rats. Because of both the potential for HIV transmission and for serious adverse reactions in nursing infants, women should be instructed not to breastfeed if they are taking fosamprenavir. [11] [12]

Amprenavir resistance-associated mutations at positions I54L/M, V32I, I47V, and M46I have been detected in HIV isolates from antiretroviral-naive patients treated with fosamprenavir. No such mutations were detected in antiretroviral-naive patients treated with fosamprenavir/ritonavir. [13] [14]

Adverse Events/Toxicity

In clinical studies, 19% of patients treated with fosamprenavir developed skin rash. Most rashes were of mild to moderate intensity; fewer than 1% of patients receiving fosamprenavir developed a severe or life-threatening rash (Grade 3 or 4), including Stevens-Johnson syndrome.

Fosamprenavir calcium



Adverse Events/Toxicity (cont.)

Fosamprenavir should be discontinued in patients with severe or life-threatening rash or with moderate rash accompanied by systemic reactions.[15]

The most common treatment-emergent adverse effects in clinical studies were mild to moderate diarrhea, nausea, vomiting, and headache.[16] Oral paresthesia, abdominal pain, and depressive symptoms or mood disorders also were reported.[17]

Body fat accumulation and redistribution, hyperlipidemia, increased bleeding in hemophilia patients, hyperglycemia, exacerbation of existing diabetes mellitus, and new onset diabetes mellitus have been reported in patients receiving protease inhibitors, including fosamprenavir.[18] [19]

Drug and Food Interactions

Fosamprenavir may be taken with or without food.[20]

Coadministration of fosamprenavir with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious events is contraindicated. Specifically, coadministration of fosamprenavir with dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, pimoziide, midazolam, and triazolam is contraindicated.[21] [22]

If fosamprenavir is coadministered with ritonavir, flecainide and propafenone are also contraindicated.[23]

Serious or life-threatening drug interactions could occur between fosamprenavir and amiodarone, systemic lidocaine, bepridil, tricyclic antidepressants, or quinidine. If these agents are used concomitantly with fosamprenavir, drug concentrations should be monitored.[24] [25]

Rifampin should not be used in combination with fosamprenavir because it reduces plasma concentrations of amprenavir by about 90%.[26]

Concomitant use of products containing St. John's wort (*Hypericum perforatum*) with amprenavir or

other protease inhibitors (PIs) is not recommended. St. John's wort is expected to substantially decrease drug plasma levels and may lead to loss of virologic response and possible resistance to amprenavir or other PIs.[27]

Concomitant use of fosamprenavir with lovastatin or simvastatin is not recommended. Caution should be used when any PI, including fosamprenavir, is used concurrently with other HMG-CoA reductase inhibitors (statins) that are metabolized by the CYP3A4 pathway (for example, atorvastatin or cerivastatin). The resulting increased concentration of statins may increase the risk of myopathy or rhabdomyolysis.[28] [29]

Caution should be used when prescribing phosphodiesterase (PDE5) inhibitors for erectile dysfunction (sildenafil or vardenafil) in patients receiving PIs, including fosamprenavir. Coadministration of a PI with sildenafil or vardenafil may substantially increase PDE5 inhibitor concentrations and associated adverse effects, including hypotension, visual changes, and priapism.[30]

Carbamazepine, phenobarbital, and phenytoin should be used cautiously in combination with fosamprenavir. These anticonvulsants may decrease fosamprenavir effectiveness by decreasing amprenavir plasma levels.[31]

Contraindications

Fosamprenavir is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to amprenavir.[32]

Fosamprenavir should be used with caution in patients with a known sulfonamide allergy. Fosamprenavir contains a sulfonamide moiety. The potential for cross-sensitivity between drugs in the sulfonamide class and fosamprenavir is unknown.[33]

Clinical Trials

For information on clinical trials that involve Fosamprenavir calcium, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Fosamprenavir calcium AND

Fosamprenavir calcium



Clinical Trials (cont.)

HIV Infections.

Dosing Information

Mode of Delivery: Oral.[34]

Dosage Form: Tablets containing 700 mg fosamprenavir.[35]

The recommended dose of fosamprenavir for treatment-naïve adult patients is either 1) 1,400 mg twice daily without ritonavir, 2) 1,400 mg once daily plus ritonavir 200 mg once daily, or 3) 700 mg twice daily plus ritonavir 100 mg twice daily. The recommended dose of fosamprenavir for PI-experienced adult patients is 700 mg twice daily plus ritonavir 100 mg twice daily. An additional 100 mg/day of ritonavir is recommended when efavirenz is administered with fosamprenavir/ritonavir once daily.[36]

In patients with mild or moderate hepatic impairment (Child-Pugh score of 5 to 8), a fosamprenavir dosage of 700 mg twice daily without ritonavir is recommended. Fosamprenavir should not be used in patients with severe hepatic impairment (Child-Pugh score of 9 to 12), since the dose of fosamprenavir cannot be reduced below 700 mg.[37]

Safety and efficacy for pediatric dosing have not been established.[38]

Storage: Store at 25 C (77 F); excursions permitted to 15 C to 30 C (59 F to 86 F).[39]

Chemistry

CAS Name: Carbamic acid, [(1S,2R)-3-[[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1-(phenylmethyl)-2-(phosphonoxy)propyl]-, C-[(3S)-tetrahydro-3-furanyl] ester, calcium salt[40]

CAS Number: 226700-81-8[41]

Molecular formula: C₂₅H₃₄CaN₃O₉P₁S[42]

C48.2%, H5.5%, N6.7%, O23.1%, P5.0%, S5.1%,

Ca6.4%[43]

Molecular weight: 623.64[44]

Physical Description: Fosamprenavir calcium is a white to cream-colored solid.[45]

Solubility: Approximately 0.31 mg/ml in water at 25 C.[46]

Other Names

GW433908[47]

908[48]

f-APV[49]

Further Reading

Wood R, Arasteh K, Stellbrink HJ, et al. Six-week randomized controlled trial to compare the tolerabilities, pharmacokinetics, and antiviral activities of GW433908 and amprenavir in human immunodeficiency virus type 1-infected patients. *Antimicrob Agents Chemother* 2004 Jan;48(1):116-23. PMID: 14693528

Becker S, Thornton L. Fosamprenavir: advancing HIV protease inhibitor treatment options. *Expert Opin Pharmacother* 2004 Sep;5(9):1995-2005. PMID: 15330736

MacManus S, Yates PJ, Elston RC, White S, Richards N, Snowden W. GW433908/ritonavir once daily in antiretroviral therapy-naïve HIV-infected patients: absence of protease resistance at 48 weeks. *AIDS* 2004 Mar 5;18(4):651-5. PMID: 15090770

Vierling P, Greiner J. Prodrugs of HIV protease inhibitors. *Curr Pharm Des* 2003;9(22):1755-70. PMID: 12871195

Fosamprenavir calcium



Manufacturer Information

Fosamprenavir calcium
Vertex Pharmaceuticals Inc
130 Waverly Street
Cambridge, MA 02139-4242
(617) 577-6000

Fosamprenavir calcium
GlaxoSmithKline
5 Moore Drive
Research Triangle Park, NC 27709
(888) 825-5249

Lexiva
GlaxoSmithKline
5 Moore Drive
Research Triangle Park, NC 27709
(888) 825-5249

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

References

1. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 1. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
2. GlaxoSmithKline - Lexiva Prescribing Information, May 2004. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
3. FDA - Lexiva Application Acceptance Letter. Available at: <http://www.fda.gov/cder/foi/appletter/2003/21548ltr.pdf>. Accessed 09/03/04.
4. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 1. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
5. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 3. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
6. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 4. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
7. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 5. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
8. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 5. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.

Fosamprenavir calcium



9. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 24. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
10. AHFS Drug Information - 2004; p. 623
11. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 24. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
12. AHFS Drug Information - 2004; p. 623
13. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 2. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
14. Vertex Pharmaceuticals. - Lexiva Product Information. Available at: <http://www.vpharm.com/Lexiva.html>. Accessed 09/27/04.
15. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 25. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
16. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 25. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
17. USP DI Online - Fosamprenavir (Systemic). Available at: http://www.uspdi.micromedex.com/v1/updates/new/foxamprenavir_april_2004.pdf, p. 3. Accessed 09/02/04.
18. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, pp. 16-17. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
19. USP DI Online - Fosamprenavir (Systemic). Available at: http://www.uspdi.micromedex.com/v1/updates/new/foxamprenavir_april_2004.pdf, p. 3. Accessed 09/02/04.
20. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 5. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
21. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 15. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
22. AHFS Drug Information - 2004; p. 631
23. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 15. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
24. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 15. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
25. USP DI Online - Fosamprenavir (Systemic). Available at: http://www.uspdi.micromedex.com/v1/updates/new/foxamprenavir_april_2004.pdf, pp. 2-3. Accessed 09/02/04.
26. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 15. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
27. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 15. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
28. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 15. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
29. AHFS Drug Information - 2004; p. 631
30. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, pp. 15-16. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
31. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 21. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
32. AHFS Drug Information - 2004; p. 631
33. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 16. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
34. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 29. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
35. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 29. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
36. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 29. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
37. AHFS Drug Information - 2004; p. 631
38. AHFS Drug Information - 2004; p. 630
39. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 29. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.

Fosamprenavir calcium



40. USPD - 2003; p. 383
41. USPD - 2003; p. 383
42. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 1. Available at http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
43. Calculation. -
44. USPD - 2003; p. 383
45. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 1. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
46. GlaxoSmithKline - Lexiva Prescribing Information, May 2004, p. 1. Available at: http://us.gsk.com/products/assets/us_lexiva.pdf. Accessed 09/02/04.
47. ChemIDplus. - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp>. Accessed 09/27/04.
48. AIDS - 2004 Mar 5;18(4):651-5
49. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection - MMWR 2002;51 (No.RR-7) Updated as a Living Document on January 20, 2004. Available at: <http://aidsinfo.nih.gov/>