concentrations by about 2 $\log_{10}$ copies/ml, and CD4+ cell counts increased by about 100 cells/mm^3. This was similar to the antiviral effects of amprenavir 1200 mg twice daily. With these results, the 1395 mg twice-daily dose was selected for further development (Wood *et al.*, 2004b). The GlaxoSmith-Kline (GSK) study APV 10006 demonstrated bioequivalence between the 465- and 700-mg tablets formulations, which led to the selection of 700-mg tablet formulation for further clinical trials.

5d. Excretion

Less than 1% of amprenavir is excreted unchanged in the urine and feces. Amprenavir is metabolized in the liver by the CYP3A4 enzyme system, primarily via oxidation and to a lesser degree, by conjugation. Other CYP isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP2E1) are not involved. Although amprenavir can inhibit or induce CYP3A4, it primarily exerts inhibitory effects at clinically relevant concentrations (Hester *et al.*, 2006; Wire *et al.*, 2006b). The two major metabolites of amprenavir result from the oxidation of the tetrahydrofuran and aniline moieties, and these are the major metabolites recovered in urine and feces. There are other metabolites in lower concentrations (Sadler *et al.*, 2001a; Sadler, 2001b; Sadler, 2001c; Sadler, 2001d). The plasma elimination half-life of amprenavir is approximately 7.7 hours.

5e. Drug interactions

The drug interactions seen with fosamprenavir or fosamprenavir–ritonavir are due mainly to the effects of these agents on the CYP3A4 system. The number of drug interactions is large and the reader should check current literature including the most recent fosamprenavir package insert for up to date information.

Amprenavir is essentially an inhibitor of CYP3A4, but it is also an inducer and a substrate for the same enzyme. The plasma concentrations of some drugs can be increased to potentially life-threatening levels if co-administered with fosamprenavir. Such drugs (astemizole, cisapride, dihydroergotamine, midazolam, pimozide, bepridil, terfenadine, lovastatin, simvastatin, and triazolam) should not be administered concurrently with fosamprenavir (see Table 244.3). For other drugs, such as calcium channel blockers, atorvastatin, and phosphodiesterase inhibitors (sildenafil, tadalafil, and vardenafil), concurrent administration is permissible provided lower doses are used and there is close monitoring for toxicity (see Table 244.4). Steroids such as beclomethasone that are not metabolized by CYP3A4 enzymes should be preferred over those that are metabolized by the CYP3A4 enzymes, such as fluticasone or budesonide. Concomitant use of these latter steroids with ritonavir can lead to elevated cortisol levels and predispose to adrenal insufficiency if the corticosteroid is withdrawn (Pessanha *et al.*, 2007; see Table 244.3 and Table 244.4). Clarithromycin increases amprenavir AUC by only 18% so no dosage adjustments are needed (Brophy *et al.*, 2000). The plasma concentration of warfarin is potentially affected by all protease inhibitors including fosamprenavir (Table 244.5).

Drugs that lower the exposure to amprenavir if co-administered include the anticonvulsants phenobarbital, phenytoin, and carbamazepine (see Table 244.6). In this scenario, consideration should be given to alternative anticonvulsants.

Table 244.3. Drug interactions with fosamprenavir: contraindications.

Drug class	Drug name(s)	Reason
Antibiotics	Rifampicin, rifapentine	Decreased efficacy of fosamprenavir/amprenavir, concentration decreased by 90%
Antifungals	Voriconazole[a]	Significant reductions in voriconazole caused by ritonavir
Antimalarials	Halofantrine	Arrhythmia
HMG-CoA reductase inhibitors	Lovastatin, simvastatin	Rhabdomyolysis and toxic myopathy
Antihistamines	Astemizole, terfenadine	Arrhythmia
Antipsychotics/neuroleptics	Pimozide	Arrhythmia
Benzodiazepines	Midazolam, triazolam	Prolonged sedation and respiratory depression
Antiarrhythmics	Flecainide,[a] propafenone,[a] bepridil, encainide	Arrhythmia
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Peripheral vasospasm, ischemia
Prokinetics	Cisapride	Cardiac arrhythmia
Corticosteroids	Fluticasone	Significant exposure to corticosteroids
Hormonal contraceptives	Ethinyl estradiol,[a] norethindrone[a]	Hepatic transaminase elevations
Antiretroviral drugs	Delavirdine; etravirine	Loss of antiviral efficacy due to suboptimal levels of delavirdine; etravirine increases amprenavir levels significantly (AUC 69%, C_{min} 77%)
Herbal supplements	St. John's wort	Loss of antiviral efficacy due to suboptimal levels of amprenavir

[a]Contraindicated if ritonavir is co-administered; cautious use advised if fosamprenavir is administered without ritonavir.
Abbreviations: AUC: area-under-the-concentration-time curve; C_{min}: minimum concentration.