Table 244.5. Drugs whose concentrations may increase or decrease when used with fosamprenavir (with or without ritonavir).

| Drug class | Drug name(s) | Comment |
|---|---|---|
| Opioids | Methadone | Methadone dosage may have to be increased; amprenavir levels may be reduced |
| Anticoagulants | Coumadin (warfarin) | Risk of bleeding; requires close monitoring of international normalized ratio (INR) |

evaluated in 19 healthy volunteers. The amprenavir AUC and $C_{min}$ in the subjects who received fosamprenavir–ritonavir plus esomeprazole decreased only by 4% and 2%, respectively. In contrast, in the subjects who received atazanavir–ritonavir plus esomeprazole, significant reductions in atazanavir exposure occurred, including four subjects (21%) with over 50% reduction in atazanavir AUC and $C_{min}$. Based on these findings, fosamprenavir can be co-administered with antacids or proton pump inhibitors without a need for dose modification or separation. The co-administration of ranitidine and fosamprenavir caused moderate reductions in amprenavir AUC; hence, caution is needed if these drugs are to be co-administered.

## OTHER ANTIRETROVIRAL DRUGS

### *Nucleoside analog reverse transcriptase inhibitors*

The metabolism of nucleoside reverse transcriptase inhibitors occurs via pathways that are not influenced by CYP3A4 enzymes, hence there are no notable pharmacokinetic interactions between nucleoside reverse transcriptase inhibitors and unboosted or ritonavir-boosted fosamprenavir. No dose modification is needed when fosamprenavir is co-administered with nucleoside reverse transcriptase inhibitors. The safety and efficacy of standard dosages of fosamprenavir–ritonavir plus abacavir and lamivudine has been demonstrated (Gathe *et al.*, 2004; Rodriguez-French *et al.*, 2004). Also, co-administration of tenofovir with fosamprenavir–ritonavir 1400/100 mg daily did not alter amprenavir AUC or $C_{max}$, and there was no significant change in ritonavir AUC. In combination with fosamprenavir–ritonavir 1400/100 mg daily, however, tenofovir led to a nonsignificant increase in ritonavir AUC, although amprenavir AUC remained unchanged (Kurowski *et al.*, 2007). Similarly, tenofovir and emtricitabine given along with fosamprenavir–ritonavir 1400/200 mg daily did not result is any clinically meaningful interaction. The AUC and $C_{min}$ for amprenavir were 21% and 18% higher than historical controls, respectively; and the AUCs for tenofovir and emtricitabine were within 7% of historical control values (Parks *et al.*, 2007).

Table 244.6. Drugs that can reduce or increase plasma concentrations of amprenavir (fosamprenavir)

| Drugs that can increase amprenavir concentrations | Drugs that can decrease amprenavir concentrations |
|---|---|
| Indinavir | Efavirenz[a] |
| Nelfinavir | Nevirapine[b] |
| Etravirine[c] | Lopinavir–ritonavir |
| | Saquinavir |
| | Carbamazepine |
| | Dexamethasone |
| | Phenobarbital |
| | Phenytoin |
| | Primidone |
| | Cimetidine, famotidine, nizatidine, ranitidine ($H_2$-receptor agonists) Antacids |

[a]If efavirenz is co-administered, use fosamprenavir 1400 mg/ritonavir 300 mg once daily or fosamprenavir 700 mg/ritonavir 100 mg twice daily.
[b]Nevirapine should not be used with fosamprenavir 1400 mg twice daily; no dose adjustment required if ritonavir is co-administered.
[c]Contraindicated.

### *Nonnucleoside analog reverse transcriptase inhibitors*

Chronic administration of nevirapine leads to induction of CYP450 metabolism. The concurrent use of nevirapine (200 mg twice daily) and unboosted fosamprenavir (1400 mg twice daily) is contraindicated because that combination is associated with a 33% reduction in the pharmacokinetic parameters of amprenavir (−33% for AUC, −25% for $C_{max}$, and −35% for $C_{min}$), and increased exposure to nevirapine (DeJesus *et al.*, 2006). However, ritonavir-boosted fosamprenavir 700/100 mg twice daily can be co-administered with nevirapine without dosage adjustments because there was no significant change in amprenavir AUC or $C_{max}$ with this combination, although $C_{min}$ decreased by 19% (DeJesus *et al.*, 2006).

Efavirenz 600 mg daily can be co-administered with fosamprenavir– ritonavir 700/100 mg twice daily without any dose change because no significant pharmacokinetic changes occurred at steady state. This contrasts with the findings when fosamprenavir–ritonavir 1400/200 mg daily was co-administered with efavirenz 600 mg daily. This latter regimen resulted in reductions in amprenavir AUC and trough plasma concentrations by 13% and 36%, respectively. However, co-administration of 600 mg efavirenz with fosamprenavir–ritonavir 1400/300 mg daily resulted in amprenavir plasma concentrations that were similar to those achieved with treatment with fosamprenavir–ritonavir 1395/200 mg daily (Wire *et al.*, 2004). Accordingly, an extra 100 mg of ritonavir should be added (making a total daily dose of 300 mg) if efavirenz is co-administered with the once-daily regimen of fosamprenavir–ritonavir.

The clinical use of delavirdine had faded to near obscurity by the time fosamprenavir became approved for clinical use. As such, there are no published studies of drug interactions between these agents. However, co-administration of