al., 1996), the clinical evidence for additive or synergistic effects is weak (Drew, 2006).

The combination of foscarnet and penciclovir was synergistic against HSV-1 and additive against type HSV-2 (Sutton *et al.*, 1992). No other *in vitro* or clinical data are available.

HIV-1 replication has been reported to be additively or synergistically inhibited when foscarnet is combined with zidovudine (Eriksson and Schinazi, 1989; Koshida *et al.*, 1989; Chrisp and Clissold, 1991; Snoeck *et al.*, 1992) or with either didanosine or zalcitabine (Palmer *et al.*, 1996), and an additive or synergistic effect has been found between foscarnet and interferon-alpha (Hartshorn *et al.*, 1986; Degre and Beck, 1994). Some evidence for at least additive activity was found in a small clinical trial in which HIV-infected patients who were on zidovudine for a minimum of several months were given a short course of intravenous foscarnet; patients experienced a decline in plasma HIV virus concentration (in this case, assessed by p24 antigenemia) (Jacobson *et al.*, 1988).

Additive inhibition of the duck hepadnavirus *in vitro* was shown by combinations of ganciclovir and foscarnet at clinically achievable concentrations (Civitico *et al.*, 1996).

A recent report has suggested that valproic acid inhibits the antiviral effect of foscarnet (as well as that of ganciclovir and cidofovir) when human CMV is grown in human umbilical vein endothelial cells (Michaelis *et al.*, 2008). Whether this is of *in vivo* significance has not been assessed.

3. MECHANISM OF DRUG ACTION

Foscarnet inhibits the DNA polymerases (both DNA dependent and RNA dependent, the latter usually called reverse transcriptases) of several virus families. Unlike nucleoside and nucleotide antiviral drugs, foscarnet does not require intracellular alteration for its activity.

Foscarnet inhibits the DNA polymerase of herpesviruses by binding at a site where pyrophosphate is removed as the DNA chain grows by addition of nucleoside triphosphates (Sarin *et al.*, 1985; Oberg, 1986). Addition of a deoxynucleoside triphosphate to the growing DNA chain releases a pyrophosphate during this process. Foscarnet selectively inhibits the viral DNA polymerase, without significantly inhibiting other cellular enzymes (Wagstaff and Bryson, 1994). Similarly, foscarnet inhibits the reverse transcriptase of HIV-1 (Sarin *et al.*, 1985) and duck hepatitis virus (Sherker *et al.*, 1986). Inhibition is reversed when infected cells are no longer exposed to the compound.

Studies have analyzed the effect of various inhibitors on the steps of HIV-1 reverse transcription (Hooker *et al.*, 2001). Foscarnet and a nucleoside analog inhibited both early and late synthesis of single negative-strand DNA. At the molecular level, the mechanism of action of foscarnet appears to be to stabilize the HIV reverse transcriptase in a pretranslocational state (before adding the nucleotide triphosphate), trapping it there (Marchand *et al.*, 2007; Meyer *et al.*, 2007). Susceptibility to foscarnet was reduced by reverse transcriptase mutations, such as E89K, which are biased toward the posttranslational state. In contrast, a bound nucleotide traps the reverse transcriptase in a posttranslational state, so it continues to add to the DNA chain (Marchand *et al.*, 2007).

The hydrophobicity of the amino acid at position 90 of reverse transcriptase has been described as being critical for binding of foscarnet to the enzyme (Im *et al.*, 1993). However, this may not be correct, as codon 90 is not located within the deoxyribonucleotide triphosphate (dNTP) binding site. The mechanism is most likely due to template binding repositioning, as described for mutations within codons 88, 92, and 156 (Tachedjian *et al.*, 1995).

4. MODE OF DRUG ADMINISTRATION AND DOSAGE

4a. Adults

INTRAVENOUS ADMINISTRATION

For induction therapy in patients infected with susceptible viruses it is recommended that foscarnet be given in a dose of 120–180 mg/kg/day in two or three divided doses for 2–3 weeks of induction therapy and at 90–120 mg/kg/day for maintenance therapy (see Table 219.6). Foscarnet dosing must be adjusted for renal function (see section 4d, Those requiring altered dosages). Because foscarnet has extremely poor oral absorption and poor oral tolerability at the doses required, it must be administered by controlled intravenous infusion, the only approved route of administration. In addition, because it is an irritant and associated with thrombophlebitis, foscarnet is preferably administered via a central venous catheter, and via a peripheral vein only if that route is unavailable. The drug does not need to be diluted before administration via a central line, but must be diluted to 12 mg/ml with 5% dextrose in water (a 1:2 dilution) if it is to be

Table 219.6. Recommended doses of foscarnet for treatment of HSV and VZV infections, and for induction and treatment of CMV infections.

	HSV or VZV treatment	CMV induction	CMV maintenance
CrCl ml//min/kg	dose (mg/kg) every 8 hours	dose (mg/kg) every 8 hours	Daily dose
> 1.6	40	60	90–120
1.4–1.6	37	55	90–120
1.2–1.4	33	49	78–104
1.0–1.2	28	42	75–100
0.8–1.0	24	35	71–94
0.6–0.8	19	28	63–84
0.4–0.6	14	21	57–76
< 0.4	Not recommended	Not recommended	Not recommended

Abbreviations: HSV: herpes simplex virus; VZV: varicella-zoster virus; CMV: cytomegalovirus; CrCl: creatine clearance.
Source: Data from Clinigen Healthcare (2014).