Interactions
In order to reduce the risk of inflammation, intra-ocular use of fomivirsen is not recommended within 2 to 4 weeks of cidofovir treatment.

Antiviral Action
Fomivirsen is an antisense oligonucleotide that inhibits human CMV replication. It is active against strains of CMV resistant to ganciclovir, foscarnet, and cidofovir. Resistance to fomivirsen has been induced *in vitro*, but cross-resistance to antivirals with other modes of action is unlikely.

Uses and Administration
Fomivirsen is an antisense oligonucleotide that has been used as the sodium salt for the local treatment of CMV retinitis (p.853) in patients with AIDS. For newly diagnosed disease, a dose of 165 micrograms has been given by intravitreal injection into the affected eye once each week for 3 weeks, then on alternate weeks thereafter. For previously treated disease, 330 micrograms has been injected into the affected eye; this dose may be repeated once after 2 weeks and then once every 4 weeks thereafter.

◊ Reviews.

1. Perry CM, Barman Balfour JA. Fomivirsen. *Drugs* 1999; **57:** 375–80.
2. Geary RS, *et al.* Fomivirsen: clinical pharmacology and potential drug interactions. *Clin Pharmacokinet* 2002; **41:** 255–60.

Preparations
Proprietary Preparations (details are given in Part 3)
Ger.: Vitravene†; ***Switz.:*** Vitravene†; ***USA:*** Vitravene†.

Fosamprenavir Calcium *(USAN, rINNM)*

Calcii Fosamprenavirum; Fosamprenavir cálcico; Fosamprénavir Calcique; GW-433908G. (3*S*)-Tetrahydro-3-furyl{(α*S*)-α-[(1*R*)-1-hydroxy-2-(*N*^{1}-isobutylsulfanilamido)ethyl]phenethyl}carbamate calcium phosphate (1:1).

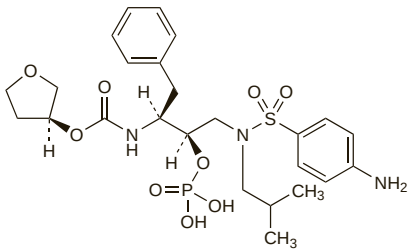
Кальций Фосампренавир

$C_{25}H_{36}CaN_3O_9PS$ = 625.7.

CAS — 226700-79-4 (fosamprenavir); 226700-81-8 (fosamprenavir calcium).

ATC — J05AE07.

ATC Vet — QJ05AE07.



(fosamprenavir)

Adverse Effects and Precautions
As for Amprenavir, p.865.

Interactions
Drugs interacting with amprenavir (p.866) might reasonably also be expected to interact with fosamprenavir.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p.883 and Table 1, p.917.

Antiviral Action
As for Amprenavir (see p.866). Fosamprenavir is a prodrug that is rapidly hydrolysed to amprenavir (p.865) by cellular phosphatases in the gut epithelium as it is absorbed. Fosamprenavir itself has little or no antiviral activity *in vitro*

Pharmacokinetics
After oral doses, fosamprenavir is rapidly hydrolysed to amprenavir in the gastrointestinal epithelium as it is absorbed. Peak plasma concentrations of amprenavir are attained after 1.5 to 4 hours. Fosamprenavir may be given with or without food. For details of the pharmacokinetics of amprenavir, see p.866.

◊ Reviews.

1. Wire MB, *et al.* Fosamprenavir: clinical pharmacokinetics and drug interactions of the amprenavir prodrug. *Clin Pharmacokinet* 2006; **45:** 137–68.

Uses and Administration
Fosamprenavir is a prodrug of amprenavir, which is an HIV-protease inhibitor with antiviral activity against HIV. Fosamprenavir is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when fosamprenavir is used alone, and it is therefore used with other antiretrovirals.

Fosamprenavir may be given with or without food. It is given orally as the calcium salt, but doses are expressed in terms of the base. Fosamprenavir calcium 748 mg is equivalent to about 700 mg of fosamprenavir or to 600 mg of amprenavir and 50 mg of fosamprenavir solution is equivalent to about 43 mg of amprenavir.

In the UK, the recommended dose of ritonavir-boosted fosamprenavir in both treatment-experienced and treatment-naive adult patients is fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg twice daily.

In the USA, recommended doses in treatment-naive adult patients are:

- fosamprenavir 1.4 g twice daily *without ritonavir*, or
- fosamprenavir 1.4 g once daily *plus* ritonavir 200 mg once daily, or
- fosamprenavir 1.4 g once daily *plus* ritonavir 100 mg once daily, or
- fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg twice daily

The recommended dose in treatment-experienced patients is fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg twice daily.

For details of doses in children and adolescents, see below.

Doses should be reduced in patients with mild or moderate hepatic impairment (see below).

◊ Reviews.

1. Chapman TM, *et al.* Fosamprenavir: a review of its use in the management of antiretroviral therapy-naive patients with HIV infection. *Drugs* 2004; **64:** 2101–24.
2. Hester EK, *et al.* Fosamprenavir: drug development for adherence. *Ann Pharmacother* 2006; **40:** 1301–10.

Administration in children. For the treatment of HIV infection in children and adolescents, fosamprenavir is given daily with other antiretroviral drugs. Doses are based on body-weight and should not exceed the adult dose.

In the UK, the recommended dose of fosamprenavir oral solution in children and adolescents weighing 25 to 38 kg is 18 mg/kg twice daily *plus* ritonavir oral solution 3 mg/kg twice daily. Children and adolescents weighing at least 39 kg may be given the adult fosamprenavir tablet dose, see above. It is not licensed for use in children below 25 kg in weight or 6 years of age.

In the USA, the recommended dose of fosamprenavir oral suspension in treatment-naive children 2 to 5 years of age is fosamprenavir 30 mg/kg twice daily. Treatment-naive children 6 years of age or older may be given fosamprenavir 30 mg/kg twice daily or 18 mg/kg twice daily *plus* ritonavir 3 mg/kg twice daily. Treatment-experienced patients 6 years of age or older may be given fosamprenavir 18 mg/kg twice daily *plus* ritonavir 3 mg/kg twice daily.

Ritonavir 100-mg capsules may be given to children and adolescents taking fosamprenavir oral suspension if they weigh at least 33 kg.

Administration in hepatic impairment. Fosamprenavir should be used with caution in all patients with hepatic impairment.

UK licensed product information recommends:

- in patients with mild hepatic impairment (Child-Pugh score 5 to 6): fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg once daily
- in patients with moderate hepatic impairment (Child-Pugh score 7 to 9): fosamprenavir 450 mg twice daily *plus* ritonavir 100 mg once daily

US licensed product information recommends:

- in treatment-naive patients with mild hepatic impairment (Child-Pugh score 5 to 6): fosamprenavir 700 mg twice daily *without ritonavir*, or *plus* ritonavir 100 mg once daily
- in treatment-experienced patients with mild hepatic impairment (Child-Pugh score 5 to 6): fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg once daily
- in treatment-naive patients with moderate hepatic impairment (Child-Pugh score 7 to 9): fosamprenavir 700 mg twice daily *without ritonavir*, or fosamprenavir 450 mg twice daily *plus* ritonavir 100 mg once daily
- in treatment-experienced patients with moderate hepatic impairment (Child-Pugh score 7 to 9): fosamprenavir 450 mg twice daily *plus* ritonavir 100 mg once daily
- in treatment-naive patients with severe hepatic impairment (Child-Pugh score 10 to 12): fosamprenavir 350 mg twice daily *without ritonavir*

Fosamprenavir *plus* ritonavir should not be used in patients with severe hepatic impairment.

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Telzir; ***Austral.:*** Telzir; ***Belg.:*** Telzir; ***Canad.:*** Telzir; ***Cz.:*** Telzir; ***Denm.:*** Telzir; ***Fin.:*** Telzir; ***Fr.:*** Telzir; ***Ger.:*** Telzir; ***Gr.:*** Telzir; ***Hung.:*** Telzir; ***Irl.:*** Telzir; ***Israel:*** Lexiva; ***Ital.:*** Telzir; ***Mex.:*** Telzer; ***Neth.:*** Telzir; ***Norw.:*** Telzir; ***Pol.:*** Telzir; ***Port.:*** Telzir; ***Spain:*** Telzir; ***Swed.:*** Telzir; ***Switz.:*** Telzir; ***UK:*** Telzir; ***USA:*** Lexiva.

Foscarnet Sodium *(BAN, USAN, rINN)*

A-29622; EHB-776 (anhydrous and hexahydrate); Foscarnet sódico; Foscarnet Sodique; Foscarnet sodique hexahydraté; Foscarnetum Natricum; Foscarnetum natricum hexahydricum; Foskarneettinatriumheksahydraatti; Foskarnet sodná sůl hexahydrát; Foskarnet Sodyum; Foskarnetnatriumhexahydrat; Foskarneto natrio druska heksahidratas; Foszkarnet-nátrium; Phosphonatoformate Trisodium; Phosphonoformate Trisodium. Trisodium phosphonatoformate hexahydrate.

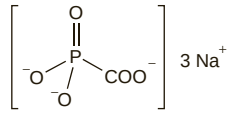
Фоскарнет Натрий

$CNa_3O_5P,6H_2O$ = 300.0.

CAS — 63585-09-1 (foscarnet sodium); 34156-56-4 (foscarnet sodium hexahydrate).

ATC — J05AD01.

ATC Vet — QJ05AD01.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Foscarnet Sodium Hexahydrate; Foscarnet Sodium BP 2008). A white or almost white crystalline powder. Soluble in water; practically insoluble in alcohol. A 2% solution in water has a pH of 9.0 to 11.0. Protect from light.

Incompatibility. Foscarnet sodium has been found to be visually incompatible with some commonly used injectable drugs including amphotericin B, aciclovir sodium, co-trimoxazole, ganciclovir, and pentamidine isetionate;[1,2] licensed product information also lists incompatibilities with vancomycin, glucose 30% solution, and solutions containing calcium. It is therefore recommended that foscarnet should not be infused via an intravenous line with any other drug.

1. Lor E, Takagi J. Visual compatibility of foscarnet with other injectable drugs. *Am J Hosp Pharm* 1990; **47:** 157–9.
2. Baltz JK, *et al.* Visual compatibility of foscarnet with other injectable drugs during simulated Y-site administration. *Am J Hosp Pharm* 1990; **47:** 2075–7.

Adverse Effects and Treatment
The most serious common adverse effect of foscarnet sodium is renal impairment, which may be severe. Anaemia may be common and granulocytopenia and thrombocytopenia have been reported. Foscarnet can chelate bivalent metal ions, and may be associated with an acute decrease in ionised calcium in the plasma that is not necessarily reflected by measurements of total calcium; the decrease is proportional to the rate of infusion. Other electrolyte disturbances may occur. Some patients may have convulsions. Excretion of high concentrations in the urine can cause local irritation and genital ulceration. Other adverse effects reported include nausea, vomiting, diarrhoea, malaise, fatigue, fever, headache, dizziness, paraesthesia, tremor, mood disturbances, rash, abnormal liver function tests, blood pressure and ECG changes, and isolated reports of pancreatitis. Intravenous injection may cause phlebitis at the site of injection.

In cases of overdosage it is important to maintain hydration. Foscarnet elimination may be increased by haemodialysis.

Effects on the CNS. Convulsions may occur in up to 10% of AIDS patients receiving foscarnet and have been reported after overdoses. Contributing factors include underlying CNS pathol-

ogy (HIV-related encephalopathy or other infections) and foscarnet-related electrolyte disturbances. However, seizures have occurred in patients without apparent risk factors.[1]

1. Lor E, Liu YQ. Neurologic sequelae associated with foscarnet therapy. *Ann Pharmacother* 1994; **28:** 1035–7.

Effects on electrolyte balance. Acute hypocalcaemia has been reported to occur in about 30% of AIDS patients receiving foscarnet. Other electrolyte disturbances include hypokalaemia and hypomagnesaemia (each in about 15%), hypophosphataemia (8%), and hyperphosphataemia (6%). Hypocalcaemia may cause paraesthesias and, together with hypomagnesaemia and hypokalaemia, may predispose to seizures and cardiovascular disturbances.

Electrolyte abnormalities (increased calcium, magnesium, phosphate, and potassium requirements, and a reduction in the need for sodium) have been reported to be dramatically accelerated by foscarnet in a patient being given total parenteral nutrition.[1]

1. Matarese LE, *et al.* Foscarnet-induced electrolyte abnormalities in a bone marrow transplant patient receiving parenteral nutrition. *J Parenter Enteral Nutr* 2000; **24:** 170–3.

Effects on the kidneys. The most serious common adverse effect of foscarnet sodium is nephrotoxicity. Clinically significant increases in serum-creatinine concentrations occur in about 30% of patients, and the incidence of nephrotoxicity tends to increase with increasing dose[1] and with duration of therapy.[2] Foscarnet sodium is excreted unchanged in the urine and tubulointerstitial lesions and deposition of crystals in the glomerular capillary lumen have been implicated.[3] Acute renal failure has occurred and haemodialysis has been reported to have reduced plasma-foscarnet concentrations.[4] The risk of nephrotoxicity can be minimised by ensuring adequate hydration, the use of intermittent dosing schedules,[5] and by adjusting the dose according to serum-creatinine concentrations. Nephrogenic diabetes insipidus and renal tubular acidosis associated with foscarnet have been reported.[6-8]

1. Jacobson MA, *et al.* A dose-ranging study of daily maintenance intravenous foscarnet therapy for cytomegalovirus retinitis in AIDS. *J Infect Dis* 1993; **168:** 444–8.
2. Gaub J, *et al.* The effect of foscarnet (phosphonoformate) on human immunodeficiency virus isolation, T-cell subsets and lymphocyte function in AIDS patients. *AIDS* 1987; **1:** 27–33.
3. Beaufils H, *et al.* Foscarnet and crystals in glomerular capillary lumens. *Lancet* 1990; **336:** 755.
4. Deray G, *et al.* Foscarnet-induced acute renal failure and effectiveness of haemodialysis. *Lancet* 1987; **ii:** 216.
5. Deray G, *et al.* Prevention of foscarnet nephrotoxicity. *Ann Intern Med* 1990; **113:** 332.
6. Farese RV, *et al.* Nephrogenic diabetes insipidus associated with foscarnet treatment of cytomegalovirus retinitis. *Ann Intern Med* 1990; **112:** 955–6.
7. Conn J, *et al.* Nephrogenic diabetes insipidus associated with foscarnet—a case report. *J Antimicrob Chemother* 1996; **37:** 1180–1.
8. Navarro JF, *et al.* Nephrogenic diabetes insipidus and renal tubular acidosis secondary to foscarnet therapy. *Am J Kidney Dis* 1996; **27:** 431–4.

Effects on the skin and mucous membranes. A generalised pruritic macular rash was reported in a patient given foscarnet, which subsided after the drug was withdrawn.[1]

There have been several reports of genital ulceration,[2-7] possibly related to local toxicity arising from high concentrations of foscarnet in the urine. Oral ulceration, usually with genital ulceration, has occurred during foscarnet treatment.[3-5] Uvular and oesophageal ulcerations have also been reported.[4,8]

1. Green ST, *et al.* Generalised cutaneous rash associated with foscarnet usage in AIDS. *J Infect* 1990; **21:** 227–8.
2. Van Der Pijl JW, *et al.* Foscarnet and penile ulceration. *Lancet* 1990; **335:** 286.
3. Gilquin J, *et al.* Genital and oral erosions induced by foscarnet. *Lancet* 1990; **335:** 287.
4. Fégueux S, *et al.* Penile ulcerations with foscarnet. *Lancet* 1990; **335:** 547.
5. Moyle G, *et al.* Penile ulcerations with foscarnet. *Lancet* 1990; **335:** 547–8.
6. Lacey HB, *et al.* Vulval ulceration associated with foscarnet. *Genitourin Med* 1992; **68:** 182.
7. Caumes E, *et al.* Foscarnet-induced vulvar erosion. *J Am Acad Dermatol* 1993; **28:** 799.
8. Saint-Marc T, *et al.* Uvula and oesophageal ulcerations with foscarnet. *Lancet* 1992; **340:** 970–1.

Precautions

Foscarnet sodium should be used with caution in renal impairment and doses should be reduced if serum creatinine is raised. Serum-creatinine concentrations should be measured on alternate days throughout induction treatment; monitoring may be weekly during maintenance therapy. An adequate state of hydration must be maintained during therapy to prevent renal toxicity. Electrolytes, especially calcium and magnesium, should also be monitored and deficiencies corrected before and during foscarnet therapy.

Electrolyte content. Each g of foscarnet sodium (hexahydrate) represents about 10 mmol of sodium and about 3.3 mmol of phosphate.

Interactions

Foscarnet should not be given with other nephrotoxic drugs such as aminoglycosides, amphotericin B, and ciclosporin, or with other drugs that can affect serum-calcium concentrations. Intravenous pentamidine can produce both of these effects and severe additive toxicity may result from its use with foscarnet; fatalities have occurred.

Ciprofloxacin. Tonic-clonic seizures associated with foscarnet use in 2 patients receiving multiple antimicrobial drugs were thought to have been exacerbated by the concurrent use of ciprofloxacin.[1]

1. Fan-Havard P, *et al.* Concurrent use of foscarnet and ciprofloxacin may increase the propensity for seizures. *Ann Pharmacother* 1994; **28:** 869–72.

Parenteral nutrition. For mention that foscarnet may exacerbate the need for electrolyte replacement in patients receiving total parenteral nutrition see Effects on Electrolyte Balance, above.

Antiviral Action

Foscarnet inhibits replication of human herpesviruses including CMV, herpes simplex virus types 1 and 2, herpesvirus 6, Epstein-Barr virus, and varicella-zoster virus. Activity is also reported against hepatitis B virus and HIV. Foscarnet acts by inhibition of virus-specific DNA polymerases and reverse transcriptases: unlike the nucleoside reverse transcriptase inhibitors and ganciclovir, foscarnet does not require intracellular conversion to an active triphosphate.

◊ References.

1. Balfour HH, *et al.* Effect of foscarnet on quantities of cytomegalovirus and human immunodeficiency virus in blood of persons with AIDS. *Antimicrob Agents Chemother* 1996; **40:** 2721–6.
2. Jabs DA, *et al.* Incidence of foscarnet resistance and cidofovir resistance in patients treated for cytomegalovirus retinitis. *Antimicrob Agents Chemother* 1998; **42:** 2240–4.

Pharmacokinetics

The pharmacokinetics of foscarnet are complicated by the high incidence of renal impairment induced during therapy and by the deposition and subsequent gradual release of foscarnet from bone. Thus the estimation of half-life depends upon the duration of foscarnet therapy and the duration of the observation period. The plasma half-life in patients with normal renal function is about 2 to 4 hours, but terminal half-lives up to about 8 days have been reported when accumulation in bone has taken place. Plasma protein binding is about 14 to 17%. Foscarnet crosses the blood-brain barrier in variable amounts; CSF concentrations ranging from zero to more than 3 times the plasma concentration have been reported. Foscarnet is mostly excreted unchanged in the urine mainly through glomerular filtration.

◊ In 13 HIV-infected male patients with lymphadenopathy or AIDS-related complex[1] foscarnet [sodium] by continuous intravenous infusion (0.14 to 0.19 mg/kg per minute) produced plasma-foscarnet concentrations of about 100 to 500 nanomol/mL. There appeared to be a link between the degree of adverse effects experienced and plasma-foscarnet concentrations above 350 nanomol/mL. Foscarnet was excreted mainly via the kidneys. It was thought that up to 20% of the cumulative intravenous dose may have been deposited in bone 7 days after the end of infusion.

Penetration of foscarnet into the CSF is very variable and in 5 patients[1] CSF concentrations of foscarnet were found to be 13 to 68% of those in the plasma. Subsequent studies showed that CSF concentrations of foscarnet would be virostatic in most patients,[2] attaining a mean concentration of about 25% of plasma concentration after a single infusion[2,3] and 66% under steady state conditions.[3] CSF concentrations ranged from 0 to 340%[2] and 5 to 72%[3] of those in plasma. There was a correlation between the amount of foscarnet in the CSF and inflammation of the meninges in one study,[2] and with the HIV infection stage in another,[3] but neither reported a correlation with plasma concentration.

1. Sjövall J, *et al.* Pharmacokinetics of foscarnet and distribution to cerebrospinal fluid after intravenous infusion in patients with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1989; **33:** 1023–31.
2. Raffi F, *et al.* Penetration of foscarnet into cerebrospinal fluid of AIDS patients. *Antimicrob Agents Chemother* 1993; **37:** 1777–80.
3. Hengge UR, *et al.* Foscarnet penetrates the blood-brain barrier: rationale for therapy of cytomegalovirus encephalitis. *Antimicrob Agents Chemother* 1993; **37:** 1010–14.

Uses and Administration

Foscarnet is a non-nucleoside pyrophosphate analogue active against herpesviruses. It is used as the trisodium salt mainly for the treatment of CMV retinitis in AIDS patients and for aciclovir-resistant mucocutaneous herpes simplex virus infections in immunocompromised patients (see below).

Foscarnet is given by intravenous infusion. A solution containing foscarnet sodium 24 mg/mL may be given via a central vein or diluted with glucose 5% or sodium chloride 0.9% to a concentration of 12 mg/mL and given via a peripheral vein. Hydration with 0.5 to 1 litre of sodium chloride 0.9% is recommended with each infusion to reduce renal toxicity.

For the treatment of **CMV retinitis** in patients with normal renal function, the usual dose is 60 mg/kg infused over at least 1 hour every 8 hours, or 90 mg/kg infused over 1½ to 2 hours every 12 hours, for 2 to 3 weeks; this should then be followed by maintenance therapy with 60 mg/kg daily, increasing to 90 to 120 mg/kg daily infused over 2 hours if tolerated.

For the treatment of aciclovir-resistant mucocutaneous **herpes simplex virus infections** in patients with normal renal function, a dose of 40 mg/kg, infused over at least 1 hour every 8 or 12 hours is given for 2 to 3 weeks or until lesions have healed.

Doses of foscarnet should be reduced in patients with renal impairment (see below).

◊ Reviews.

1. Chrisp P, Clissold SP. Foscarnet: a review of its antiviral activity, pharmacokinetic properties and therapeutic use in immunocompromised patients with cytomegalovirus retinitis. *Drugs* 1991; **41:** 104–29.
2. Wagstaff AJ, Bryson HM. Foscarnet: a reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic use in immunocompromised patients with viral infections. *Drugs* 1994; **48:** 199–226.

Administration in renal impairment. Doses of intravenous foscarnet sodium may need to be reduced in patients with renal impairment. The following doses, given every 8 hours, are suggested by the UK licensed product information according to creatinine clearance (CC):

treatment of CMV retinitis:

- CC more than 1.6 mL/kg per minute: 60 mg/kg
- CC 1.6 to 1.4 mL/kg per minute: 55 mg/kg
- CC 1.4 to 1.2 mL/kg per minute: 49 mg/kg
- CC 1.2 to 1.0 mL/kg per minute: 42 mg/kg
- CC 1.0 to 0.8 mL/kg per minute: 35 mg/kg
- CC 0.8 to 0.6 mL/kg per minute: 28 mg/kg
- CC 0.6 to 0.4 mL/kg per minute: 21 mg/kg
- CC less than 0.4 mL/kg per minute: use not recommended

treatment of aciclovir-resistant mucocutaneous herpes simplex infections:

- CC more than 1.6 mL/kg per minute: 40 mg/kg
- CC 1.6 to 1.4 mL/kg per minute: 37 mg/kg
- CC 1.4 to 1.2 mL/kg per minute: 33 mg/kg
- CC 1.2 to 1.0 mL/kg per minute: 28 mg/kg
- CC 1.0 to 0.8 mL/kg per minute: 24 mg/kg
- CC 0.8 to 0.6 mL/kg per minute: 19 mg/kg
- CC 0.6 to 0.4 mL/kg per minute: 14 mg/kg
- CC less than 0.4 mL/kg per minute: use not recommended

In the USA modification of doses by extending the dose interval has been recommended, resulting in proportional reductions in daily dose similar to those in the UK.

Cytomegalovirus infections. Foscarnet is used in the treatment of severe CMV infections (p.853) in immunocompromised patients and appears to possess similar efficacy to ganciclovir[1] (see also under Ganciclovir, p.880). It has been particularly useful in patients who require antiretroviral therapy for AIDS and are unable to tolerate ganciclovir (because of haematological toxicity). For patients unable to tolerate systemic therapy foscarnet has been tried as an intravitreal injection.[2-4] Beneficial responses have been reported with various regimens including intravitreal injections of foscarnet 1.2 mg every 48 hours for 4 doses[2] or induction with 2.4 mg twice weekly[4] or every 72 hours for 6 doses,[3] then once weekly maintenance thereafter.[3,4] Combined treatment with foscarnet and ganciclovir each given intravitreally has also been reported to be effective;[5] however, although combination systemic therapy has been widely used where resistance to ganciclovir is suspected, the evidence for a synergistic effect against CMV is not very strong.[6]

Foscarnet has also been investigated for primary prophylaxis of CMV infection in bone marrow transplant recipients at high risk of infection.[7,8]

1. Reusser P, *et al.* Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Randomized multicenter trial of foscarnet versus ganciclovir for preemptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation. *Blood* 2002; **99:** 1159–64.
2. Lieberman RM, *et al.* Efficacy of intravitreal foscarnet in a patient with AIDS. *N Engl J Med* 1994; **330:** 868–9.

3. Diaz-Llopis M, *et al.* High dose intravitreal foscarnet in the treatment of cytomegalovirus retinitis in AIDS. *Br J Ophthalmol* 1994; **78:** 120–4.
4. Ausayakhun S, *et al.* Intravitreal foscarnet for cytomegalovirus retinitis in patients with AIDS. *J Med Assoc Thai* 2005; **88:** 103–7.
5. Velez G, *et al.* High-dose intravitreal ganciclovir and foscarnet for cytomegalovirus retinitis. *Am J Ophthalmol* 2001; **131:** 396–7.
6. Drew WL. Is combination antiviral therapy for CMV superior to monotherapy? *J Clin Virol* 2006; **35:** 485–8.
7. Ippoliti C, *et al.* Foscarnet for prevention of cytomegalovirus infection in allogeneic marrow transplant recipients unable to receive ganciclovir. *Bone Marrow Transplant* 1997; **20:** 491–5.
8. Bregante S, *et al.* Foscarnet prophylaxis of cytomegalovirus infections in patients undergoing allogeneic bone marrow transplantation (BMT): a dose-finding study. *Bone Marrow Transplant* 2000; **26:** 23–9.

Herpes simplex infections. Although foscarnet is effective in the treatment of herpes simplex infections it is usually reserved for severe or disseminated herpes simplex infections, particularly in immunocompromised patients who have infections resistant to aciclovir (see p.854). A 2% cream applied topically is effective in the treatment of refractory herpes simplex infections of the skin,[1] and is licensed for such use in some countries. Topical use of a 1% foscarnet cream has also been investigated.[2]

1. Gross G, Braun D. Wirksamkeit und Verträglichkeit von topisch appliziertem Foscarnet-Natrium bei der Behandlung von Herpes labialis. Ergebnisse einer Anwendungsbeobachtung. *Hautarzt* 2006; **57:** 40–6.
2. Javaly K, *et al.* Treatment of mucocutaneous herpes simplex virus infections unresponsive to acyclovir with topical foscarnet cream in AIDS patients: a phase I/II study. *J Acquir Immune Defic Syndr* 1999; **21:** 301–6.

Varicella-zoster infections. Foscarnet is the recommended treatment for aciclovir-resistant varicella-zoster infections (p.855). In a study[1] of 5 patients with AIDS and aciclovir-resistant zoster infection complete healing was reported for 3 patients after treatment with foscarnet 120 mg/kg daily for 14 to 26 days. Two patients relapsed 7 and 14 days respectively after stopping treatment. In another study[2] 10 of 13 HIV-infected patients with aciclovir-resistant zoster infection had complete healing after treatment with 100 mg/kg twice daily of foscarnet for 12 to 30 days. Five of the patients relapsed after stopping treatment with the median time to relapse being 110 days.

1. Safrin S, *et al.* Foscarnet therapy in five patients with AIDS and acyclovir-resistant varicella-zoster virus infection. *Ann Intern Med* 1991; **115:** 19–21.
2. Breton G, *et al.* Acyclovir-resistant herpes zoster in human immunodeficiency virus-infected patients: results of foscarnet therapy. *Clin Infect Dis* 1998; **27:** 1525–7.

Preparations

BP 2008: Foscarnet Intravenous Infusion.

Proprietary Preparations (details are given in Part 3)

Austral.: Foscavir; ***Austria:*** Foscavir; ***Belg.:*** Foscavir; ***Braz.:*** Foscavir; ***Cz.:*** Foscavir†; ***Fr.:*** Foscavir; ***Ger.:*** Foscavir; Triapten; ***Gr.:*** Foscavir; ***Hung.:*** Foscavir; ***Israel:*** Foscavir; ***Ital.:*** Foscavir; ***Jpn:*** Foscavir; ***Neth.:*** Foscavir; ***Norw.:*** Foscavir; ***NZ:*** Foscavir; ***Port.:*** Foscavir; ***Spain:*** Foscavir; ***Swed.:*** Foscavir; ***Switz.:*** Foscavir; ***UK:*** Foscavir; ***USA:*** Foscavir.

Ganciclovir *(BAN, USAN, rINN)*

BIOLF-62; BN-B759V; BW-759; BWB-759U; BW-759U; DHPG; Dihydroxypropoxymethylguanine; 9-(1,3-Dihydroxy-2-propoxymethyl)guanine; Ganciclovirum; Gancyklovir; Gansikloviiri; Gansiklovir; 2′-NDG; 2′-Nor-2′-deoxyguanosine; RS-21592. 9-[2-Hydroxy-1-(hydroxymethyl)ethoxymethyl]guanine.

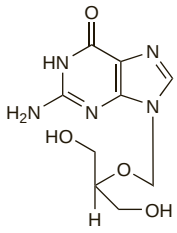
Ганцикловир

$C_9H_{13}N_5O_4$ = 255.2.

CAS — 82410-32-0.

ATC — J05AB06; S01AD09.

ATC Vet — QJ05AB06; QS01AD09.



Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Ganciclovir). A white to off-white crystalline powder. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Ganciclovir Sodium *(BANM, USAN, rINNM)*

Ganciclovir sódico; Ganciclovir Sodique; Natrii Ganciclovirum.

Натрий Ганцикловир

$C_9H_{12}N_5NaO_4$ = 277.2.

CAS — 107910-75-8.

ATC — J05AB06; S01AD09.

ATC Vet — QJ05AB06; QS01AD09.

Incompatibility. Ganciclovir is reported to be incompatible with foscarnet.

Stability. Ganciclovir sodium solution in sodium chloride 0.9% was found[1] to be stable when stored in polypropylene infusion-pump syringes for 12 hours at 25° and for 10 days at 4°. Little variation was found in ganciclovir concentration after storage of a 2% solution at room temperature, 5°, and –8° for 10 to 24 days.[2]

1. Mulye NV, *et al.* Stability of ganciclovir sodium in an infusion-pump syringe. *Am J Hosp Pharm* 1994; **51:** 1348–9.
2. Morlet N, *et al.* High dose intravitreal ganciclovir for CMV retinitis: a shelf life and cost comparison study. *Br J Ophthalmol* 1995; **79:** 753–5.

Adverse Effects and Treatment

The most common adverse effects of systemic ganciclovir are haematological and include neutropenia and thrombocytopenia; anaemia also occurs. Neutropenia affects up to 50% of patients given ganciclovir, most commonly starting in the first or second week of use. It is usually reversible but may be prolonged or irreversible and can lead to potentially fatal infections. AIDS patients may be at a greater risk of neutropenia than other immunosuppressed patients. Thrombocytopenia occurs in about 20% of patients given ganciclovir. Those with iatrogenic immunosuppression may be more at risk of developing thrombocytopenia than AIDS patients. Other adverse effects occurring in patients given systemic ganciclovir include dyspnoea, headache, fever, rash, pruritus, asthenia, CNS and gastrointestinal disturbances, infection, increased serum-creatinine concentration, and abnormal liver function tests. Less frequent adverse effects reported include anaphylaxis, arrhythmias, hypotension, pancreatitis, haematuria, as well as metabolic, musculoskeletal, urogenital, and cutaneous symptoms. When given intravenously, irritation or phlebitis may occur at the site of injection due to the high pH.

Local adverse effects have been associated with the insertion of ocular implants of ganciclovir.

Animal studies have suggested that there may be a risk of adverse testicular effects with temporary or permanent inhibition of spermatogenesis. Female fertility may also be affected. Such studies also suggest that ganciclovir is a potential mutagen, teratogen, and carcinogen.

Haemodialysis and hydration may be useful in reducing plasma concentrations of ganciclovir. Haematological adverse effects may be reversed in some patients by stopping treatment or reducing dosage; blood cell counts should return to normal within 3 to 7 days.

Colony-stimulating factors have been given with ganciclovir to limit its haematological toxicity.

Effects on the blood. Ganciclovir-induced neutropenia was successfully treated in a patient with CMV retinitis and bone-marrow suppression by intravenous *molgramostim* 5 micrograms/kg.[1] In a multicentre, randomised placebo-controlled study[2] in 69 AIDS patients with CMV infection who developed neutropenia from ganciclovir therapy, *lenograstim* given in a dose of 50 micrograms/m^2 subcutaneously yielded similar positive results.

1. Russo CL, *et al.* Treatment of neutropenia associated with dyskeratosis congenita with granulocyte-macrophage colony-stimulating factor. *Lancet* 1990; **336:** 751–2.
2. Dubreuil-Lemaire M-L, *et al.* Lenograstim for the treatment of neutropenia in patients receiving ganciclovir for cytomegalovirus infection: a randomised, placebo-controlled trial in AIDS patients. *Eur J Haematol* 2000; **65:** 337–43.

Effects on mental function. Psychosis has been associated with intravenous ganciclovir use in 2 patients with normal renal function.[1,2] In both cases, psychotic symptoms such as agitation, confusion, and hallucination, occurred within 2 to 6 days of starting treatment with ganciclovir; symptoms resolved after ganciclovir was stopped.

1. Hansen BA, *et al.* Ganciclovir-induced psychosis. *N Engl J Med* 1996; **335:** 1397.
2. Southworth MR, Dunlap SH. Psychotic symptoms and confusion associated with intravenous ganciclovir in a heart transplant recipient. *Pharmacotherapy* 2000; **20:** 479–83.

Effects on the skin. An interstitial granulomatous drug reaction was reported[1] in a 57-year old woman after about one month of treatment with intravenous ganciclovir for CMV pneumonia. No other new drugs were given before the onset of the lesions and they resolved spontaneously within 2 weeks of stopping the ganciclovir.

1. Marcollo Pini A, *et al.* Interstitial granulomatous drug reaction following intravenous ganciclovir. *Br J Dermatol* 2008; **158:** 1391–3.

Precautions

Ganciclovir should be used with caution in patients with renal impairment and doses should be adjusted according to creatinine clearance. It should not be given by rapid or bolus injection and adequate hydration should be maintained during intravenous infusion. It should be given with caution to patients with low blood counts or with a history of cytopenic reactions to drugs. Complete blood and platelet counts should be performed every 2 days or daily during the first 14 days of intravenous therapy and once weekly thereafter; ganciclovir should be withdrawn if the neutrophil count falls below 500 cells/microlitre or the platelet count falls below 25 000 cells/microlitre. Patients receiving oral ganciclovir should also be monitored regularly.

Ganciclovir is contra-indicated in pregnancy; contraception is recommended during ganciclovir treatment and, additionally for men, for 90 days thereafter. Adverse effects have occurred in the offspring of *animals* given ganciclovir during pregnancy and lactation.

Because of the risk of carcinogenicity and the high pH of the solution, contact with the skin and eyes should be avoided during the reconstitution of ganciclovir sodium injection.

Sodium content. Each g of ganciclovir sodium represents about 3.6 mmol of sodium.

Interactions

Zidovudine given with ganciclovir may have an additive neutropenic effect and should not normally be given during intravenous ganciclovir induction therapy, although it has been given with caution during oral maintenance therapy. Probenecid and other drugs that inhibit renal tubular secretion and resorption may reduce the renal clearance of ganciclovir, and so increase its serum concentrations. Use of intravenous ganciclovir with oral mycophenolate mofetil may result in increased plasma concentrations of both drugs due to competition for renal tubular secretion. Drugs that inhibit rapid cell division such as amphotericin B, some antineoplastic drugs, co-trimoxazole, dapsone, flucytosine, hydroxycarbamide, nucleoside analogues, and pentamidine may have additive toxic effects if given with ganciclovir. Convulsions have been reported when ganciclovir was given with imipenem and cilastatin.

Antivirals. Additive haematological toxicity, including neutropenia, may occur if ganciclovir is given with *zidovudine* (see Zidovudine, p.915), and there are reports of increased plasma concentrations of *didanosine* when given with ganciclovir (see p.871). There has also been a report[1] of decreased blood concentrations of ganciclovir when didanosine (200 mg every 12 hours) was given orally 2 hours before oral ganciclovir (1 g every 8 hours) but not when the two drugs were given at the same time. However, a later study[2] using twice the dose of oral ganciclovir found no effect irrespective of whether ganciclovir was given 2 hours before or 2 hours after didanosine.

When ganciclovir was given orally with *zalcitabine*, a 22% increase in the area under the concentration-time curve for ganciclovir was noted although it was believed that this did not necessitate any dosage modification.[3] No pharmacokinetic changes were reported when ganciclovir was given orally with *stavudine*.[3]

1. Cimoch PJ, *et al.* Pharmacokinetics of oral ganciclovir alone and in combination with zidovudine, didanosine, and probenecid in HIV-infected subjects. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; **17;** 227–34.
2. Jung D, *et al.* Effect of high-dose oral ganciclovir on didanosine disposition in human immunodeficiency virus (HIV)-positive patients. *J Clin Pharmacol* 1998; **38:** 1057–62.
3. Jung D, *et al.* The pharmacokinetics and safety profile of oral ganciclovir combined with zalcitabine or stavudine in asymptomatic HIV- and CMV-seropositive patients. *J Clin Pharmacol* 1999; **39:** 505–12.