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.

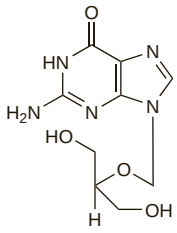
Ганцикловир

$C_9H_{13}N_5O_4$ = 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.