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.

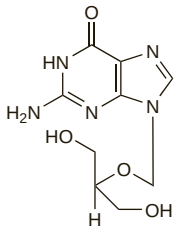
Ганцикловир

$C_9H_{13}N_5O_4$ = 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.

Ciclosporin. Reversible acute unilateral or bilateral eye movement disorders typical of sixth cranial nerve palsies[1] occurred in 4 patients who received ciclosporin and ganciclovir after bone marrow transplantation.

1. Openshaw H, *et al.* Eye movement disorders in bone marrow transplant patients on cyclosporin and ganciclovir. *Bone Marrow Transpl* 1997; **19:** 503–5.

Antiviral Action

Ganciclovir inhibits replication of human herpesviruses *in vivo* and *in vitro*. It is active against CMV, herpes simplex virus types 1 and 2, Epstein-Barr virus, varicella-zoster virus, and herpesvirus 6, 7, and 8. This activity is due to intracellular conversion of ganciclovir by viral thymidine kinase (in herpes simplex and varicella-zoster infected cells) or possibly by cellular deoxyguanosine kinase (in Epstein-Barr infected cells) to ganciclovir monophosphate with subsequent cellular conversion to the diphosphate and the active triphosphate. Ganciclovir triphosphate inhibits viral DNA synthesis by inhibiting the viral DNA polymerase enzyme as well as being incorporated into the viral DNA. This process is selective for infected cells; the concentration of ganciclovir triphosphate may be up to a hundredfold higher in CMV-infected cells than in uninfected cells.

Ganciclovir has a similar spectrum of activity to aciclovir, herpes simplex virus types 1 and 2 being the most susceptible of the herpesviruses. However, CMV is much more susceptible to ganciclovir than aciclovir.

Resistance

Resistance to ganciclovir has been found *in vitro* in herpes simplex viruses, varicella-zoster virus, and CMV. Possible mechanisms of resistance include a reduction in the phosphorylation of ganciclovir to the active form and reduced sensitivity of viral DNA polymerase. Resistance has been reported in CMV strains isolated from patients receiving ganciclovir for prolonged periods and in those with an initially high viral load. It has also been seen in AIDS patients with CMV retinitis who have never previously received the drug. Cross-resistance with cidofovir is common.

◊ The development of CMV resistance to ganciclovir may be a factor in disease progression in patients receiving prolonged therapy with ganciclovir and the incidence of resistance is reported to increase with duration of therapy.[1] A ganciclovir-resistant isolate of CMV has been detected in about 30% of 95 patients after 9 months of treatment and correlated with dissemination of infection to the contralateral eye.[2] Treatment of unilateral retinitis with systemic ganciclovir (intravenously, or orally together with an implant) was associated with a higher incidence of ganciclovir-resistant CMV infection developing in the contralateral eye, compared with treatment with ganciclovir implant alone.[3]

Ganciclovir-resistant CMV has been reported[4] to be an important cause of late morbidity in seronegative patients who received CMV-seropositive organ transplants; in one study,[5] 5 of 67 seronegative recipients developed ganciclovir-resistant CMV disease compared with none of 173 seropositive subjects.

1. Drew WL. Cytomegalovirus resistance to antiviral therapies. *Am J Health-Syst Pharm* 1996; **53** (suppl 2): S17–S23.
2. Jabs DA, *et al.* Cytomegalovirus retinitis and viral resistance: ganciclovir resistance. *J Infect Dis* 1998; **177:** 770–3.
3. Imai Y, *et al.* Emergence of drug-resistant cytomegalovirus retinitis in the contralateral eyes of patients with AIDS treated with ganciclovir. *J Infect Dis* 2004; **189:** 611–15.
4. Limaye AP. Ganciclovir-resistant cytomegalovirus in organ transplant recipients. *Clin Infect Dis* 2002; **35:** 866–72.
5. Limaye AP, *et al.* Emergence of ganciclovir-resistant cytomegalovirus disease among recipients of solid-organ transplants. *Lancet* 2000; **356:** 645–9.

Pharmacokinetics

Ganciclovir is poorly absorbed from the gastrointestinal tract after oral doses and there is minimal systemic absorption after intravitreal injection. Bioavailability of oral ganciclovir is about 5%, and is increased by intake with food to 6 to 9%. After intravenous dosage as ganciclovir sodium it is widely distributed to body tissues and fluids including intra-ocular fluid and CSF. Binding to plasma proteins is reported to be 1 to 2%. Ganciclovir is excreted unchanged in the urine mainly by glomerular filtration and also active tubular secretion. In patients with normal renal function the half-life is about 2.5 to 4.5 hours after intravenous doses and about 4 to 5.7 hours after oral doses. In patients with renal impairment, the renal clearance decreases and the half-life increases; a half-life of 28.5 hours has been reported when the serum-creatinine concentration was greater than 398 micromol/litre.

Haemodialysis has been reported to reduce plasma-ganciclovir concentrations by about 50%.

◊ References.

1. Arevalo JF, *et al.* Intravitreous and plasma concentrations of ganciclovir and foscarnet after intravenous therapy in patients with AIDS and cytomegalovirus retinitis. *J Infect Dis* 1995; **172:** 951–6.
2. Morlet N, *et al.* High dose intravitreal ganciclovir injection provides a prolonged therapeutic intraocular concentration. *Br J Ophthalmol* 1996; **80:** 214–16.
3. Lavelle J, *et al.* Effect of food on the relative bioavailability of oral ganciclovir. *J Clin Pharmacol* 1996; **36:** 238–41.
4. Zhou X-J, *et al.* Population pharmacokinetics of ganciclovir in newborns with congenital cytomegalovirus infection. *Antimicrob Agents Chemother* 1996; **40:** 2202–5.
5. Giffy KG. Pharmacokinetics of oral ganciclovir capsules in HIV-infected persons. *AIDS* 1996; **10** (suppl 4): S3–S6.
6. Jung D, *et al.* Steady-state relative bioavailability of three oral ganciclovir dosage regimens delivering 6,000 mg/day in patients with human immunodeficiency virus. *J Clin Pharmacol* 1998; **38:** 1021–4.
7. Jung D, *et al.* Absolute bioavailability and dose proportionality of oral ganciclovir after ascending multiple doses in human immunodeficiency virus (HIV)-positive patients. *J Clin Pharmacol* 1998; **38:** 1122–8.
8. Jung D, *et al.* Effect of food on high-dose oral ganciclovir disposition in HIV-positive subjects. *J Clin Pharmacol* 1999; **39:** 161–5.
9. Snell GI, *et al.* Pharmacokinetic assessment of oral ganciclovir in lung transplant recipients with cystic fibrosis. *J Antimicrob Chemother* 2000; **45:** 511–16.
10. Wiltshire H, *et al.* Pharmacokinetic profile of ganciclovir after its oral administration and from its prodrug, valganciclovir, in solid organ transplant recipients. *Clin Pharmacokinet* 2005; **44:** 495–507.
11. Asano-Mori Y, *et al.* Pharmacokinetics of ganciclovir in haematopoietic stem cell transplantation recipients with or without renal impairment. *J Antimicrob Chemother* 2006; **57:** 1004–7.

Uses and Administration

Ganciclovir is a synthetic nucleoside analogue of guanine closely related to aciclovir (p.862), but has greater activity against CMV. It is used for the treatment and suppression of life-threatening or sight-threatening CMV infections in immunocompromised patients, including those with AIDS and those with iatrogenic immunosuppression associated with organ transplantation or chemotherapy of neoplastic disease (see also below). It has also been used for superficial ocular herpes simplex infections.

Ganciclovir is given by intravenous infusion as the sodium salt but doses are expressed in terms of ganciclovir; 54.3 mg of ganciclovir sodium is equivalent to about 50 mg of ganciclovir. Solutions for infusion are usually prepared to give a concentration of ganciclovir of 50 mg/mL, then further diluted to contain not more than 10 mg/mL. An intravenous solution is given over 1 hour.

In **CMV infections**, the usual initial dose for ***treatment*** is 5 mg/kg by intravenous infusion every 12 hours for 14 to 21 days. This induction period may be followed by *maintenance* therapy to prevent recurrence or progression of the disease. The usual maintenance dosage is 5 mg/kg by intravenous infusion as a single daily dose for 7 days each week or 6 mg/kg daily for 5 days each week. If retinitis recurs or progresses a further induction course of ganciclovir may be given. AIDS patients who have received initial treatment with intravenous ganciclovir, and who have stable CMV retinitis following at least 3 weeks of intravenous therapy, may be given oral valganciclovir. In some countries oral formulations of ganciclovir sodium are available for maintenance; typical dosage is 3 g daily in divided doses.

For ***prevention*** of CMV infection in immunocompromised patients, specifically those receiving immunosuppressive therapy after organ transplantation, ganciclovir may be given in an *initial* dose of 5 mg/kg by intravenous infusion every 12 hours for 7 to 14 days, followed by intravenous *maintenance* therapy as above.

Doses of ganciclovir should be reduced in renal impairment (see below).

Intravitreal implants providing controlled release of ganciclovir are available for those patients with CMV retinitis who are unable to tolerate systemic therapy; the implants are designed to release ganciclovir over a period of 5 to 8 months.

Ganciclovir has been used as a topical ophthalmic 0.15% gel for the treatment of superficial ocular **herpes simplex infections**.

◊ General references.

1. Faulds D, Heel RC. Ganciclovir: a review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy in cytomegalovirus infections. *Drugs* 1990; **39:** 597–638.
2. Markham A, Faulds D. Ganciclovir: an update of its therapeutic use in cytomegalovirus infection. *Drugs* 1994; **48:** 455–84.
3. Crumpacker CS. Ganciclovir. *N Engl J Med* 1996; **335:** 721–9.
4. McGavin JK, Goa KL. Ganciclovir: an update of its use in the prevention of cytomegalovirus infection and disease in transplant recipients. *Drugs* 2001; **61:** 1153–83.

Administration in renal impairment. Doses of ganciclovir should be reduced in renal impairment. Licensed product information recommends the following intravenous doses based on creatinine clearance (CC):

- CC 70 mL/minute or more: 5 mg/kg every 12 hours for induction, followed by 5 mg/kg every 24 hours for maintenance
- CC 50 to 69 mL/minute: 2.5 mg/kg every 12 hours for induction, 2.5 mg/kg every 24 hours for maintenance
- CC 25 to 49 mL/minute: 2.5 mg/kg every 24 hours for induction, 1.25 mg/kg every 24 hours for maintenance
- CC 10 to 24 mL/minute: 1.25 mg/kg every 24 hours for induction, 0.625 mg/kg every 24 hours for maintenance
- dialysis patients: on days when dialysis is performed 1.25 mg/kg for induction, or 0.625 mg/kg for maintenance, in each case given shortly after the end of dialysis. In the USA, a maximum of 3 doses each week is recommended

Cytomegalovirus infections. Ganciclovir is used in both the treatment and prophylaxis of CMV infections (p.853) in immunocompromised patients although the prodrug valganciclovir, which is as effective as ganciclovir and has a more convenient oral dosage regimen, may now be preferred.

As with other herpesvirus infections, antiviral treatment tends to be suppressive rather than curative, and long-term maintenance therapy is necessary. Treatment in patients with AIDS is complicated by the additive haematological toxicity of ganciclovir and zidovudine. Clinical studies comparing ganciclovir with foscarnet for AIDS-related CMV retinopathy have shown higher mortality rates in patients given ganciclovir than in those given foscarnet.[1,2] The use of ganciclovir with CMV immunoglobulins[3,4] or normal immunoglobulins,[5] or with foscarnet[6,7] has been reported to improve both efficacy and tolerance.

An alternative is the use of *intravitreal* controlled-release ganciclovir implants[8-11] to avoid systemic adverse effects. Intravitreal ganciclovir used with intravitreal foscarnet has been reported to be effective.[12]

Oral preparations of ganciclovir have been tried for maintenance therapy and may be a useful adjunct to prevent systemic infection in patients treated with the intravitreal implants[13] (but see under Resistance, above). The use of oral ganciclovir in high doses has been investigated;[14] daily doses of up to 6 g have been reported to be of benefit, although a conclusive comparison with standard intravenous doses could not be made. CMV infections at other sites in AIDS patients, including gastrointestinal and pulmonary infections, respond less well to ganciclovir than does retinitis.

Ganciclovir is also valuable for prophylaxis and early treatment of CMV infections in *transplant recipients*.[7,15-22] It is not clear whether pre-emptive therapy in infected patients is a better strategy than prophylaxis.[23] For established infections, ganciclovir is reported to be more effective in solid organ transplant recipients than in bone marrow transplant recipients. Ganciclovir has also been tried for prevention of CMV infection in patients with AIDS, although results are conflicting.[24,25]

Treatment of *congenital infections* has a generally poor outcome. Prolonged treatment periods may improve the response, but the safety of extended treatment with ganciclovir in this age group has not been fully evaluated and there is a need for further randomised controlled studies.[26] There is some recent evidence[27] that a 6-week course started in neonates with clinically apparent disease affecting the CNS prevents hearing deterioration at 6 months and may also prevent deterioration at or beyond 1 year of age.

1. Studies of Ocular Complications of AIDS Research Group, in Collaboration with the AIDS Clinical Trials Group. Mortality in patients with the acquired immunodeficiency syndrome treated with either foscarnet or ganciclovir for cytomegalovirus retinitis. *N Engl J Med* 1992; **326:** 213–20.
2. Polis MA, *et al.* Increased survival of a cohort of patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis who received sodium phosphonoformate (foscarnet). *Am J Med* 1993; **94:** 175–80.

3. D'Alessandro AM, *et al.* Successful treatment of severe cytomegalovirus infections with ganciclovir and CMV hyperimmune globulin in liver transplant recipients. *Transplant Proc* 1989; **21:** 3560–1.
4. Salmela K, *et al.* Ganciclovir in the treatment of severe cytomegalovirus disease in liver transplant patients. *Transplant Proc* 1990; **22:** 238–40.
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7. Mylonakis E, *et al.* Combination antiviral therapy for ganciclovir-resistant cytomegalovirus infection in solid-organ transplant recipients. *Clin Infect Dis* 2002; **34:** 1337–41.
8. Anand R, *et al.* Control of cytomegalovirus retinitis using sustained release of intraocular gancyclovir. *Arch Ophthalmol* 1993; **111:** 223–7.
9. Martin DF, *et al.* Treatment of cytomegalovirus retinitis with an intraocular sustained-release ganciclovir implant: a randomized controlled clinical trial. *Arch Ophthalmol* 1994; **112:** 1531–9.
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11. Ausayakhun S, *et al.* Treatment of cytomegalovirus retinitis in AIDS patients with intravitreal ganciclovir. *J Med Assoc Thai* 2005; **88** (suppl 9): S15–S20.
12. Velez G, *et al.* High-dose intravitreal ganciclovir and foscarnet for cytomegalovirus retinitis. *Am J Ophthalmol* 2001; **131:** 396–7.
13. Martin DF, *et al.* Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. *N Engl J Med* 1999; **340:** 1063–70.
14. Lalezari JP, *et al.* High dose oral ganciclovir treatment for cytomegalovirus retinitis. *J Clin Virol* 2002; **24:** 67–77.
15. Goodrich JM, *et al.* Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. *Ann Intern Med* 1993; **118:** 173–8.
16. Winston DJ, *et al.* Ganciclovir prophylaxis of cytomegalovirus infection and disease in allogeneic bone marrow transplant recipients. *Ann Intern Med* 1993; **118:** 179–84.
17. Hibberd PL, *et al.* Preemptive ganciclovir therapy to prevent cytomegalovirus disease in cytomegalovirus antibody-positive renal transplant recipients: a randomized controlled trial. *Ann Intern Med* 1995; **123:** 18–26.
18. Winston DJ, *et al.* Randomised comparison of ganciclovir and high-dose acyclovir for long-term cytomegalovirus prophylaxis in liver-transplant recipients. *Lancet* 1995; **346:** 69–74.
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20. Singh N. Preemptive therapy versus universal prophylaxis with ganciclovir for cytomegalovirus in solid organ transplant recipients. *Clin Infect Dis* 2001; **32:** 742–51.
21. Paya CV, *et al.* Preemptive use of oral ganciclovir to prevent cytomegalovirus infection in liver transplant patients: a randomized, placebo-controlled trial. *J Infect Dis* 2002; **185:** 854–60.
22. Keven K, *et al.* Cytomegalovirus prophylaxis using oral ganciclovir or valganciclovir in kidney and pancreas-kidney transplantation under antibody preconditioning. *Transplant Proc* 2004; **36:** 3107–12.
23. Monforte V, *et al.* Preemptive therapy with intravenous ganciclovir for the prevention of cytomegalovirus disease in lung transplant recipients. *Transplant Proc* 2005; **37:** 4039–42.
24. McCarthy M. Oral ganciclovir fails to prevent CMV in HIV trial. *Lancet* 1995; **346:** 895.
25. Spector SA, *et al.* Oral ganciclovir for the prevention of cytomegalovirus disease in persons with AIDS. *N Engl J Med* 1996; **334:** 1491–7.
26. Michaels MG, *et al.* Treatment of children with congenital cytomegalovirus infection with ganciclovir. *Pediatr Infect Dis J* 2003; **22:** 504–8.
27. Kimberlin DW, *et al.* Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr* 2003; **143:** 16–25.

Epstein-Barr virus infections. There have been anecdotal reports[1-4] of some improvement in patients with Epstein-Barr virus (EBV) infection given ganciclovir, although no antiviral therapy is entirely satisfactory (p.854).

1. Pirsch JD, *et al.* Treatment of severe Epstein-Barr virus-induced lymphoproliferative syndrome with ganciclovir: two cases after solid organ transplantation. *Am J Med* 1989; **86:** 241–4.
2. Ishida Y, *et al.* Ganciclovir for chronic active Epstein-Barr virus infection. *Lancet* 1993; **341:** 560–1.
3. MacGinley R, *et al.* Epstein-Barr virus encephalitis in a renal allograft recipient diagnosed by polymerase chain reaction on cerebrospinal fluid and successfully treated with ganciclovir. *Nephrol Dial Transplant* 2001; **16:** 197–8.
4. Adams LA, *et al.* Ganciclovir and the treatment of Epstein-Barr virus hepatitis. *J Gastroenterol Hepatol* 2006; **21:** 1758–60.

Herpesvirus infections. Ganciclovir 0.15% gel is licensed in a number of countries for the treatment of superficial ocular infections with herpes simplex. In patients with herpes simplex keratitis it has been reported to be as effective as aciclovir 3% ointment,[1] the drug most commonly used in this infection (see Ocular Herpes Simplex Infections, p.854).

1. Hoh HB, *et al.* Randomised trial of ganciclovir and acyclovir in the treatment of herpes simplex dendritic keratitis: a multicentre study. *Br J Ophthalmol* 1996; **80:** 140–3.

Preparations

USP 31: Ganciclovir for Injection; Ganciclovir Oral Suspension.

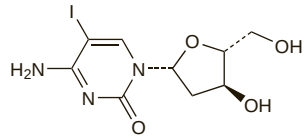
Proprietary Preparations (details are given in Part 3)
Arg.: Cigan clor; Cymevene; Cytovene†; Gasmilen; Grinevel; Virgan; ***Austral.:*** Cymevene; Vitrasert†; ***Austria:*** Cymevene; ***Belg.:*** Cymevene; Virgan; ***Braz.:*** Cymevene; Gancivir†; Ganvirax; ***Canad.:*** Cytovene; ***Chile:*** Cymevene; ***Cz.:*** Cymevene; Virgan; ***Denm.:*** Cymevene; ***Fin.:*** Cymevene; ***Fr.:*** Cymevan; Virgan; ***Ger.:*** Cymeven; ***Gr.:*** Cymevene; ***Hong Kong:*** Cymevene; ***Hung.:*** Cymevene; ***Indon.:*** Cymevene; ***Irl.:*** Cymevene; ***Israel:*** Cymevene; ***Ital.:*** Citovirax; Cymevene; ***Mex.:*** Cymevene; ***Neth.:*** Cymevene; ***Norw.:*** Cymevene; ***NZ:*** Cymevene; ***Philipp.:*** Cymevene; Virgan; ***Pol.:*** Cymevene; Virgan; ***Port.:*** Cymevene; Virgan; ***S.Afr.:*** Cymevene; ***Singapore:*** Cymevene; ***Spain:*** Cymevene; Vitrasert†; ***Swed.:*** Cymevene; ***Switz.:*** Cymevene; ***Thai.:*** Cymevene; ***Turk.:*** Cymevene; ***UK:*** Cymevene; Virgan†; ***USA:*** Cytovene; Vitrasert; ***Venez.:*** Cymevene.

Ibacitabine *(rINN)*

Ibacitabina; Ibacitabinum; Iododesoxycytidine. 2′-Deoxy-5-iodocytidine.

Ибацитабин

$C_9H_{12}IN_3O_4$ = 353.1.
CAS — 611-53-0.
ATC — D06BB08.
ATC Vet — QD06BB08.



Profile

Ibacitabine is an antiviral used topically as a 1% gel in the treatment of herpes labialis (p.854).

Preparations

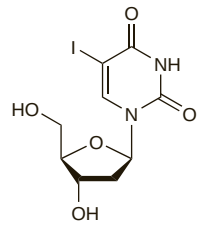
Proprietary Preparations (details are given in Part 3)
Fr.: Cuterpes.

Idoxuridine *(BAN, USAN, rINN)*

Allergan 211; GF-115; Idoksuridiini; Idoksuridinas; Idoxuridin; Idoxuridina; Idoxuridinum; IDU; 5-IDUR; 5-IUDR; NSC-39661; SKF-14287. 2′-Deoxy-5-iodouridine.

Идоксуридин

$C_9H_{11}IN_2O_5$ = 354.1.
CAS — 54-42-2.
ATC — D06BB01; J05AB02; S01AD01.
ATC Vet — QD06BB01; QJ05AB02; QS01AD01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Idoxuridine). A white or almost white crystalline powder. M.p. about 180°, with decomposition. Slightly soluble in water and in alcohol; dissolves in dilute solutions of alkali hydroxides. A 0.1% solution in water has a pH of 5.5 to 6.5. Protect from light.
USP 31 (Idoxuridine). A white, practically odourless, crystalline powder. Slightly soluble in water and in alcohol; practically insoluble in chloroform and in ether. Store in airtight containers. Protect from light.

Stability. Iodine vapour is liberated on heating idoxuridine. It has been reported that some decomposition products such as iodouracil are more toxic than idoxuridine and reduce its antiviral activity.

Adverse Effects

Hypersensitivity reactions such as irritation, pain, and pruritus may occur occasionally when idoxuridine is applied to the eyes. Other adverse effects include stinging, conjunctivitis, oedema and inflammation of the eye or eyelids, photophobia, pruritus, and rarely, occlusion of the lachrymal duct. Prolonged or excessive use may damage the cornea.

Idoxuridine applied to the skin may produce irritation, stinging, and hypersensitivity reactions. Taste disturbance may also occur. Excessive application of topical idoxuridine to the skin may cause skin maceration.

Idoxuridine is a potential carcinogen and teratogen.

Carcinogenicity. Squamous carcinoma has been reported in association with topical idoxuridine treatment.[1]

1. Koppang HS, Aas E. Squamous carcinoma induced by topical idoxuridine therapy? *Br J Dermatol* 1983; **108:** 501–3.

Precautions

Idoxuridine should be used with caution in conditions where there is deep ulceration involving the stromal layers of the cornea, as delayed healing has resulted in corneal perforation. Prolonged topical use should be avoided.

The potential teratogenicity of idoxuridine should be taken into account when treating pregnant patients or patients likely to become pregnant. Corticosteroids should be applied with caution in patients also receiving idoxuridine as they may accelerate the spread of viral infection.

Interactions

Preparations containing boric acid should not be applied to the eye in patients also receiving ocular preparations of idoxuridine as irritation ensues.

Antiviral Action

After intracellular phosphorylation to the triphosphate, idoxuridine is incorporated into viral DNA instead of thymidine so inhibiting replication of sensitive viral strains. Idoxuridine is also incorporated into mammalian DNA. Idoxuridine is active against herpes simplex and varicella zoster viruses. It has also been shown to inhibit vaccinia virus, CMV, and adenovirus.

Pharmacokinetics

Penetration of idoxuridine into the cornea and skin is reported to be poor. Idoxuridine is rapidly metabolised in the body to iodouracil, uracil, and iodide, which are excreted in the urine.

Uses and Administration

Idoxuridine is a pyrimidine nucleoside structurally related to thymidine. It is used topically in the treatment of herpes simplex keratitis and cutaneous infections with herpes simplex (p.854) and herpes zoster (see Varicella-zoster Infections, p.855), but has generally been superseded by other antivirals.

In the treatment of herpes simplex keratitis, idoxuridine is applied as a 0.1% ophthalmic solution or a 0.5% eye ointment.

Idoxuridine 5% in dimethyl sulfoxide (to aid absorption) may be painted onto the lesions of cutaneous herpes simplex and herpes zoster four times daily for 4 days.

Preparations

BP 2008: Idoxuridine Eye Drops;
USP 31: Idoxuridine Ophthalmic Ointment; Idoxuridine Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Idulea; ***Austral.:*** Herplex-D†; Stoxil; ***Belg.:*** Virexen†; ***Braz.:*** Herpesine; ***Canad.:*** Herplex; ***Ger.:*** Virunguent; Zostrum; ***Hung.:*** Oftan IDU†; ***India:*** Ridinox; ***Indon.:*** Isotic Ixodine; ***Irl.:*** Zostrum†; ***Israel:*** Virusan†; ***Ital.:*** Iducher; Idustatin; ***Malaysia:*** Virunguent†; ***Mex.:*** Idina†; ***Neth.:*** Virexen; ***NZ:*** Virasolve; ***Port.:*** Virexen†; Virunguent†; ***Rus.:*** Oftan IDU (Офтан ИДУ); ***Singapore:*** Virunguent; ***Spain:*** Virexen; ***Switz.:*** Iderpes†; Virunguent; ***UK:*** Herpid; ***Venez.:*** Herpidum†.

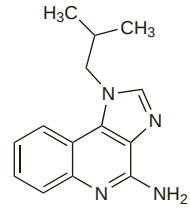
Multi-ingredient: ***Arg.:*** Itro†; ***Austral.:*** Virasolve; ***Ger.:*** Virunguent P†; ***Hong Kong:*** Virasolve†.

Imiquimod *(BAN, USAN, rINN)*

Imikimod; Imikimodi; Imiquimodum; R-837; S-26308. 4-Amino-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline.

Имихимод

$C_{14}H_{16}N_4$ = 240.3.
CAS — 99011-02-6.
ATC — D06BB10.
ATC Vet — QD06BB10.



Adverse Effects

Adverse effects after topical application of imiquimod include local skin erosion, erythema, excoriation, flaking, and oedema. There have been reports of localised hypopigmentation and hyperpigmentation. Skin reactions away from the site of application have been reported. Systemic effects after topical application include headache, flu-like symptoms, and myalgia.

Hypotension has occurred after repeated ingestion.

Hypersensitivity. Angioedema, initially of both the hands and feet and later the tongue, occurred in a 61-year-old man 3 weeks after starting treatment with a 5% imiquimod cream for squamous cell carcinoma *in situ* (Bowen's disease).[1]

1. Barton JC. Angioedema associated with imiquimod. *J Am Acad Dermatol* 2004; **51:** 477–8.

Uses and Administration

Imiquimod is an immune response modifier used topically in the treatment of external genital and perianal warts (p.1584), superficial basal cell carcinomas, and actinic keratoses (see below). For the treatment of genital and perianal **warts**, it is applied as a