may be misdiagnosed as influenza, respiratory disease, or gastroenteritis. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred rarely. Other adverse effects associated with abacavir include pancreatitis and raised liver enzyme values. Lactic acidosis, sometimes fatal and usually associated with severe hepatomegaly and steatosis, has been reported in patients receiving NRTIs.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including abacavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been observed in patients receiving antiretroviral therapy, including abacavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactatemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction such as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with NRTIs see Zidovudine, p.914.

Effects on the heart. For the possible risk of myocardial infarction in patients taking abacavir, see Effects on the Heart under Adverse Effects of Zidovudine, p.914.

Effects on the skin. Stevens-Johnson syndrome occurring in a patient receiving antiretroviral therapy with abacavir, lamivudine, and zidovudine was probably associated with abacavir.[1] Resolution occurred upon stopping antiretroviral therapy and the condition did not recur upon rechallenge with an alternative regimen also containing lamivudine and zidovudine.

1. Bossi P, *et al.* Stevens-Johnson syndrome associated with abacavir therapy. *Clin Infect Dis* 2002; **35:** 902.

Hypersensitivity. Reviews of hypersensitivity associated with abacavir.[1,2]

1. Hewitt RG. Abacavir hypersensitivity reaction. *Clin Infect Dis* 2002; **34:** 1137–42.
2. Hughes CA, *et al.* Abacavir hypersensitivity reaction: an update. *Ann Pharmacother* 2008; **42:** 387–96.

Precautions

Patients considered to be at increased risk for an abacavir hypersensitivity reaction are those that carry the human leucocyte antigen (HLA) HLA-B(*)5701 allele; screening patients for HLA-B(*)5701 allele before starting treatment with abacavir has been shown to reduce the risk of hypersensitivity reactions. Routine screening of all patients before starting treatment with an abacavir-containing product is therefore recommended. Abacavir should be stopped immediately if symptoms associated with hypersensitivity occur and should *never be restarted* in patients who have stopped therapy due to a hypersensitivity reaction. Patients should be closely monitored for signs of hypersensitivity during the first 2 months of treatment, although hypersensitivity reactions can occur at any time. Patients restarting therapy after an interruption are at particular risk even if they have not previously had symptoms of hypersensitivity. Since intermittent therapy may increase the risk of hypersensitivity developing, patients should be advised of the importance of regular dosing.

Abacavir should not be used in patients with moderate to severe hepatic impairment, and should be used with caution and reduced doses in those with lesser degrees of impairment and those with risk factors for liver disease. Treatment should be stopped if liver function deteriorates rapidly or if hepatomegaly or unexplained metabolic acidosis develop.

Abacavir should be avoided in patients with end-stage renal disease.

Interactions

Use of alcohol with abacavir may result in decreased elimination of abacavir and consequent increases in exposure. Abacavir increases the systemic clearance of oral methadone and patients should be monitored for signs of withdrawal symptoms. The dose of methadone may need to be increased in some patients.

Alcohol. References.

1. McDowell JA, *et al.* Pharmacokinetic interaction of abacavir (1592U89) and ethanol in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother* 2000; **44:** 1686–90.

Antiviral Action

Abacavir is converted intracellularly in stages to its active form carbovir triphosphate. This halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA.

◊ References.

1. Faletto MB, *et al.* Unique intracellular activation of the potent anti-human immunodeficiency virus agent 1592U89. *Antimicrob Agents Chemother* 1997; **41:** 1099–1107.

Pharmacokinetics

Abacavir is rapidly absorbed after oral doses with a bioavailability of about 80%. Absorption is delayed slightly by food but the extent is unaffected. Abacavir crosses the blood-brain barrier. It is about 50% bound to plasma proteins. The elimination half-life is about 1.5 hours after a single dose. Abacavir undergoes intracellular metabolism to the active antiviral metabolite carbovir triphosphate. Elimination is via hepatic metabolism primarily by alcohol dehydrogenase and by glucuronidation and the metabolites are excreted mainly in the urine. There is no significant metabolism by hepatic cytochrome P450 isoenzymes.

◊ References.

1. Kumar PN, *et al.* Safety and pharmacokinetics of abacavir (1592U89) following oral administration of escalating single doses in human immunodeficiency virus type 1-infected adults. *Antimicrob Agents Chemother* 1999; **43:** 603–8.
2. Hughes W, *et al.* Safety and single-dose pharmacokinetics of abacavir (1592U89) in human immunodeficiency virus type 1-infected children. *Antimicrob Agents Chemother* 1999; **43:** 609–15.
3. McDowell JA, *et al.* Multiple-dose pharmacokinetics and pharmacodynamics of abacavir alone and in combination with zidovudine in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother* 2000; **44:** 2061–7.
4. Izzedine H, *et al.* Pharmacokinetics of abacavir in HIV-1-infected patients with impaired renal function. *Nephron* 2001; **89:** 62–7.
5. Jullien V, *et al.* Abacavir pharmacokinetics in human immunodeficiency virus-infected children ranging in age from 1 month to 16 years: a population analysis. *J Clin Pharmacol* 2005; **45:** 257–64.
6. Yuen GJ, *et al.* A review of the pharmacokinetics of abacavir. *Clin Pharmacokinet* 2008; **47:** 351–71.

Uses and Administration

Abacavir is a nucleoside reverse transcriptase inhibitor with antiretroviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when abacavir is used alone, and it is therefore used with other antiretrovirals.

Abacavir is given orally as the sulfate but doses are expressed in terms of the base; 1.17 g of abacavir sulfate is equivalent to about 1 g of abacavir. The adult dose is 300 mg twice daily or 600 mg once daily. For details of doses in children, see below. Doses should be reduced in patients with hepatic impairment (see below).

Fixed-dose combination products have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing abacavir in combination with lamivudine and with lamivudine and zidovudine are available in some countries.

◊ Reviews.

1. Hervey PS, Perry CM. Abacavir: a review of its clinical potential in patients with HIV infection. *Drugs* 2000; **60:** 447–79.
2. Dando TM, Scott LJ. Abacavir plus lamivudine: a review of their combined use in the management of HIV infection. *Drugs* 2005; **65:** 285–302.
3. Castillo SA, *et al.* Long-term safety and tolerability of the lamivudine/abacavir combination as components of highly active antiretroviral therapy. *Drug Safety* 2006; **29:** 811–26.

Administration in children. For the treatment of HIV infection in children 3 months of age and older, abacavir may be given orally as a tablet or solution with other antiretroviral drugs. Doses are based on body-weight:

- 14 to 21 kg: 150 mg (half a tablet) twice daily
- 22 to 29 kg: 150 mg (half a tablet) in the morning and 300 mg (1 tablet) in the evening
- 30 kg or more: 300 mg (1 tablet) twice daily

or

- the solution may be given in a dose of 8 mg/kg twice daily to a maximum dose of 300 mg twice daily

Administration in hepatic impairment. Abacavir should not be used in patients with moderate to severe hepatic impairment, although reduced oral doses of 200 mg twice daily may be given to patients with mild impairment (Child-Pugh score 5 to 6).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Filabac; Finecil; Plusabcir; Zepril; Ziagenavir; ***Austral.:*** Ziagen; ***Austria:*** Ziagen; ***Belg.:*** Ziagen; ***Braz.:*** Ziagenavir; ***Canad.:*** Ziagen; ***Chile:*** Ziagen; ***Cz.:*** Ziagen; ***Denm.:*** Ziagen; ***Fin.:*** Ziagen; ***Fr.:*** Ziagen; ***Ger.:*** Kivexa; Ziagen; ***Gr.:*** Ziagen; ***Hong Kong:*** Ziagen; ***Hung.:*** Ziagen; ***India:*** Abamune; ***Irl.:*** Ziagen; ***Israel:*** Ziagen; ***Ital.:*** Ziagen; ***Mex.:*** Ziagenavir; ***Neth.:*** Ziagen; ***Norw.:*** Ziagen; ***NZ:*** Ziagen; ***Pol.:*** Ziagen; ***Port.:*** Ziagen; ***Rus.:*** Ziagen (Зиаген); ***S.Afr.:*** Ziagen; ***Singapore:*** Ziagen; ***Spain:*** Ziagen; ***Swed.:*** Ziagen; ***Switz.:*** Ziagen; ***Thai.:*** Ziagenavir; ***Turk.:*** Ziagen; ***UK:*** Ziagen; ***USA:*** Ziagen; ***Venez.:*** Ziagen.

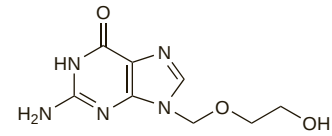
Multi-ingredient: ***Arg.:*** Kivexa; Tricivir; Trivudin; ***Austral.:*** Kivexa; Trizivir; ***Austria:*** Trizivir; ***Belg.:*** Kivexa; Trizivir; ***Canad.:*** Kivexa; Trizivir; ***Chile:*** Kivexa; Tricivir; ***Cz.:*** Kivexa; Trizivir; ***Denm.:*** Kivexa; Trizivir; ***Fin.:*** Kivexa; Trizivir; ***Fr.:*** Kivexa; Trizivir; ***Ger.:*** Trizivir; ***Gr.:*** Kivexa; Trizivir; ***Hong Kong:*** Trizivir; ***Hung.:*** Kivexa; Trizivir; ***Irl.:*** Kivexa; Trizivir; ***Israel:*** Trizivir; ***Ital.:*** Kivexa; Trizivir; ***Mex.:*** Kivexa; Trizivir; ***Neth.:*** Kivexa; Trizivir; ***Norw.:*** Kivexa; Trizivir; ***NZ:*** Kivexa; Trizivir; ***Pol.:*** Kivexa; Trizivir; ***Port.:*** Kivexa; Trizivir; ***Rus.:*** Trizivir (Тризивир); ***S.Afr.:*** Trizivar; ***Singapore:*** Trizivir†; ***Spain:*** Kivexa; Trizivir; ***Swed.:*** Kivexa; Trizivir; ***Switz.:*** Trizivir; ***UK:*** Kivexa; Trizivir; ***USA:*** Epzicom; Trizivir; ***Venez.:*** Trizivir.

Aciclovir *(BAN, rINN)*

Acicloguanosina; Aciclovirum; Aciklovír; Aciklovir; Acikloviras; Acycloguanosine; Acyclovir *(USAN)*; Acyklowir; Asikloviiri; Asiklovir; BW-248U. 9-[(2-Hydroxyethoxy)methyl]guanine; 2-Amino-1,9-dihydro-9-(2-hydroxyethoxymethyl)-6*H*-purin-6-one.

Ацикловир

$C_8H_{11}N_5O_3$ = 225.2.
CAS — 59277-89-3.
ATC — D06BB03; J05AB01; S01AD03.
ATC Vet — QD06BB03; QJ05AB01; QS01AD03.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*
Ph. Eur. 6.2 (Aciclovir). A white to almost white crystalline powder. Slightly soluble in water; very slightly soluble in alcohol; freely soluble in dimethyl sulfoxide; soluble in dilute solutions of alkali hydroxides and mineral acids.
USP 31 (Acyclovir). A white to off-white crystalline powder. Slightly soluble in water; insoluble in alcohol; soluble in dilute hydrochloric acid. Store in airtight containers. Protect from light and moisture.

Aciclovir Sodium *(BANM, rINNM)*

Aciclovir sódico; Aciclovir Sodique; Acyclovir Sodium *(USAN)*; Natrii Aciclovirum.

Натрий Ацикловир

$C_8H_{10}N_5NaO_3$ = 247.2.
CAS — 69657-51-8.
ATC — D06BB03; J05AB01; S01AD03.
ATC Vet — QD06BB03; QJ05AB01; QS01AD03.

Incompatibility. Aciclovir is reported to be incompatible with foscarnet.[1,2]

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.

Stability. A study[1] found that aciclovir sodium solutions prepared with sodium chloride 0.9% and with dextrose 5% were stable for 7 and 21 days respectively when stored at 23°. Solutions stored at 4° were found to be stable for 35 days although subsequent storage at room temperature produced irreversible precipitation. Precipitation may also occur when freshly prepared solutions are refrigerated but the precipitate redissolves at room temperature. US licensed product information recommends that diluted solutions be used within 24 hours of preparation.

1. Zhang Y, *et al.* Stability of acyclovir sodium 1, 7, and 10 mg/mL in 5% dextrose injection and 0.9% sodium chloride injection. *Am J Health-Syst Pharm* 1998; **55:** 574–7.

Adverse Effects

Aciclovir is generally well tolerated. When given intravenously as aciclovir sodium it may cause local reactions at the injection site with inflammation and phlebitis; these reactions may be associated with extravasation that can lead to tissue necrosis.

Renal impairment may be associated with systemic use of aciclovir in some patients; it is usually reversible and is reported to respond to hydration and/or dosage reduction or withdrawal, but may progress to acute renal failure. The risk of renal toxicity is increased by conditions favouring deposition of aciclovir crystals in the tubules such as when the patient is poorly hydrated, has existing renal impairment, or when the drug is given at a high dosage or by rapid or bolus injection. Some patients taking systemic aciclovir may have transient increases in blood concentrations of urea and creatinine although this is more acute with intravenous dosage.

Occasional adverse effects after systemic use include increased serum bilirubin and liver enzymes, haematological changes, skin rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), fever, headache, dizziness, and gastrointestinal effects such as nausea, vomiting, and diarrhoea. Anaphylaxis has been reported. Hepatitis and jaundice have been reported rarely. Reversible neurological effects including lethargy, somnolence, confusion, hallucinations, agitation, tremors, psychosis, convulsions, and coma have been reported in a small number of patients, particularly in those given intravenous aciclovir and with predisposing factors such as renal impairment; these effects may be more marked in older patients. Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome, sometimes resulting in death, have occurred in immunocompromised patients given high parenteral doses of aciclovir. Accelerated diffuse hair loss has also been reported.

Topical application of aciclovir may produce transient stinging, burning, itching, or erythema. Eye ointments may occasionally produce transient stinging, superficial punctate keratopathy, blepharitis, or conjunctivitis.

Effects on the blood. There has been no evidence of bone-marrow toxicity in patients given aciclovir after bone marrow transplantation.[1,2] However, megaloblastic haematopoiesis was seen in the bone marrow of 3 patients given aciclovir for suspected or proven herpes simplex encephalitis.[3] There has also been a report of inhibition of human peripheral blood lymphocytes in samples taken from healthy subjects given aciclovir.[4]

1. Serota FT, *et al.* Acyclovir treatment of herpes zoster infections: use in children undergoing bone marrow transplantation. *JAMA* 1982; **247:** 2132–5.
2. Gluckman E, *et al.* Oral acyclovir prophylactic treatment of herpes simplex infection after bone marrow transplantation. *J Antimicrob Chemother* 1983; **12** (suppl B): 161–7.
3. Amos RJ, Amess JAL. Megaloblastic haemopoiesis due to acyclovir. *Lancet* 1983; **i:** 242–3.
4. Tauris P, *et al.* Evaluation of the acyclovir-induced modulation of the plaque-forming cell response of human peripheral blood lymphocytes. *J Antimicrob Chemother* 1984; **13:** 71–7.

Effects on the kidneys. Aciclovir is excreted mostly by the kidney, and reaches high concentrations in the tubular lumen, but is relatively insoluble in urine and may therefore cause intratubular precipitation of crystals in the kidney. High doses, volume depletion, or pre-existing renal impairment increase the risk of aciclovir-associated acute renal failure, which has been reported in 12 to 48% of patients in some series. Although usually asymptomatic there may be nausea, vomiting, and flank pain, together with haematuria and pyuria. Most patients recover on stopping the drug and volume replacement, though some need temporary dialysis; use of a loop diuretic may be helpful in some cases. Slow infusion and adequate hydration can help to prevent crystal precipitation, and doses should be reduced in patients with underlying renal impairment.[1]

There are also occasional reports of renal toxicity apparently unrelated to crystal precipitation.[2-4]

1. Perazella MA. Crystal-induced acute renal failure. *Am J Med* 1999; **106:** 459–65.
2. Giustina A, *et al.* Low-dose acyclovir and acute renal failure. *Ann Intern Med* 1988; **108:** 312.
3. Eck P, *et al.* Acute renal failure and coma after a high dose of oral acyclovir. *N Engl J Med* 1991; **325:** 1178.
4. Johnson GL, *et al.* Acute renal failure and neurotoxicity following oral acyclovir. *Ann Pharmacother* 1994; **28:** 460–3.

Effects on the nervous system. Neurotoxicity, including tremor, confusion, myoclonus, agitation, lethargy, or hallucination, is an uncommon adverse effect of aciclovir, and may be hard to distinguish from progression of the underlying disease state. Renal impairment may increase the risk, although no clear relationship with peak plasma concentrations has been demonstrated; cases are also more common in elderly patients and those taking other neurotoxic drugs.[1] Of 143 patients given aciclovir by intravenous infusion in doses ranging from 0.75 to 3.6 g/m^2 daily for the treatment of herpesvirus infections after bone marrow transplantation, 6 developed reversible neurological symptoms including tremor, agitation, nausea, lethargy, mild disorientation, autonomic instability, hemiparaesthesia, and slurred speech.[2] EEGs were diffusely abnormal in all 6. Symptoms improved in all patients on withdrawing aciclovir; reinstituting aciclovir in 2 produced a recurrence of symptoms. Concomitant therapy included irradiation and methotrexate intrathecally for all 6, interferon alfa for 3, and ciclosporin for 1.

1. Ernst ME, Franey RJ. Acyclovir- and ganciclovir-induced neurotoxicity. *Ann Pharmacother* 1998; **32:** 111–13.
2. Wade JC, Meyers JD. Neurologic symptoms associated with parenteral acyclovir treatment after marrow transplantation. *Ann Intern Med* 1983; **98:** 921–5.

Effects on the skin. A report of vesicular lesions associated with intravenous use of aciclovir in a patient thought to have herpes simplex encephalitis.[1] Careful evaluation is necessary to differentiate the reaction from herpetic lesions.

1. Buck ML, *et al.* Vesicular eruptions following acyclovir administration. *Ann Pharmacother* 1993; **27:** 1458–9.

Vasculitis. Aciclovir has been associated with vasculitis. In one patient[1] it was one of many drugs given that may have caused a necrotising vasculitis. In another report an immunocompromised child with chickenpox given aciclovir by infusion developed a vasculitic rash which diminished on withdrawal of the drug.[2]

For a report of peripheral neuropathy associated with vasculitis due to the prodrug valaciclovir, see Effects on the Nervous System, p.911.

1. von Schulthess GK, Sauter C. Acyclovir and herpes zoster. *N Engl J Med* 1981; **305:** 1349.
2. Platt MPW, Eden OB. Vasculitis in association with chickenpox treatment in childhood acute lymphoblastic leukaemia. *Lancet* 1982; **ii:** 763–4.

Precautions

Systemic aciclovir should be used with caution and in reduced doses in patients with renal impairment. The elderly and patients with existing renal impairment should be closely monitored for neurological adverse effects. Adequate hydration should be maintained in patients given parenteral or high oral doses of aciclovir. Intravenous doses should be given by infusion over one hour to avoid precipitation of aciclovir in the kidney; rapid or bolus injection should be avoided. The risk of renal impairment is increased by use with other nephrotoxic drugs. Intravenous aciclovir should also be used with caution in patients with underlying neurological abnormalities, with significant hypoxia, or with serious hepatic or electrolyte abnormalities.

Breast feeding. Aciclovir is distributed into breast milk[1-4] and in some instances higher concentrations are obtained than in maternal serum.[1-3] Licensed product information reports that a maternal oral dose of 200 mg five times daily could expose a breast-fed infant to 300 micrograms/kg daily and advises caution when giving nursing mothers aciclovir. However, no adverse effects have been seen in breast-fed infants whose mothers were taking aciclovir, and the American Academy of Pediatrics considers[5] that it is therefore usually compatible with breast feeding.

1. Lau RJ, *et al.* Unexpected accumulation of acyclovir in breast milk with estimation of infant exposure. *Obstet Gynecol* 1987; **69:** 468–71.
2. Meyer LJ, *et al.* Acyclovir in human breast milk. *Am J Obstet Gynecol* 1988; **158:** 586–8.
3. Bork K, Benes P. Concentration and kinetic studies of intravenous acyclovir in serum and breast milk of a patient with eczema herpeticum. *J Am Acad Dermatol* 1995; **32:** 1053–5.
4. Taddio A, *et al.* Acyclovir excretion in human breast milk. *Ann Pharmacother* 1994; **28:** 585–7.
5. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/04/08)

Pregnancy. The incidence of congenital abnormality and spontaneous fetal loss in 1246 cases of prenatal exposure to aciclovir did not significantly differ from those in the general population.[1]

1. Stone KM, *et al.* Pregnancy outcomes following systemic prenatal acyclovir exposure: conclusions from the International Acyclovir Pregnancy Registry, 1984-1999. *Birth Defects Res A Clin Mol Teratol* 2004; **70:** 201–7.

Sodium content. Each g of aciclovir sodium represents 4.05 mmol of sodium.

Interactions

Probenecid is reported to block the renal clearance of aciclovir. The risk of renal impairment is increased by use with other nephrotoxic drugs.

Antivirals. Use of *zidovudine* with aciclovir is not generally associated with additional toxicity.[1] However, there is a report[2] of a patient who had overwhelming fatigue when given aciclovir and zidovudine together; no such effect occurred when each drug was given alone.

Former product information for *interferon alfa-n1* reported progressive renal failure in patients also given aciclovir.

1. Tartaglione TA, *et al.* Pharmacokinetic evaluations of low- and high-dose zidovudine plus high-dose acyclovir in patients with symptomatic human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1991; **35:** 2225–31.
2. Bach MC. Possible drug interaction during therapy with azidothymidine and acyclovir for AIDS. *N Engl J Med* 1987; **316:** 547.

Xanthines. For reference to evidence that aciclovir inhibits *theophylline* metabolism, resulting in accumulation, see p.1144.

Antiviral Action

Aciclovir is active against herpes simplex virus type 1 and type 2 and against varicella-zoster virus. This activity requires intracellular conversion of aciclovir by viral thymidine kinase to the monophosphate with subsequent conversion by cellular enzymes to the diphosphate and the active triphosphate. This active form inhibits viral DNA synthesis and replication by inhibiting the herpesvirus DNA polymerase enzyme as well as being incorporated into viral DNA. This process is highly selective for infected cells. Studies in *animals* and *in vitro* have found various sensitivities but show that target viruses are inhibited by concentrations of aciclovir that are readily achieved clinically. Herpes simplex virus type 1 appears to be the most susceptible, then type 2, followed by varicella-zoster virus.

The Epstein-Barr virus and CMV are also susceptible to aciclovir to a lesser extent. However, for CMV it does not appear to be activated by thymidine kinase and may act via a different mechanism. Epstein-Barr virus may have reduced thymidine kinase activity but its DNA polymerase is very sensitive to inhibition by aciclovir triphosphate, which may account for the partial activity.

Aciclovir has no activity against latent viruses, but there is some evidence that it inhibits latent herpes simplex virus at an early stage of reactivation.

Resistance

Herpes simplex virus develops resistance to aciclovir *in vitro* and *in vivo* by selection of mutants deficient in thymidine kinase. Other mechanisms of resistance include altered substrate specificity of thymidine kinase and reduced sensitivity of viral DNA polymerase. Resistance has also been reported with varicella-zoster virus, probably by similar mechanisms.

Although occasional treatment failures have been reported, resistance has not yet emerged as a major problem in treating herpes simplex infections. However, resistant viruses are more likely to be a problem in patients with a suppressed immune response; AIDS patients may be particularly prone to aciclovir-resistant mucocutaneous herpes simplex virus infections.

Viruses resistant to aciclovir because of absence of thymidine kinase may be cross-resistant to other antivirals phosphorylated by this enzyme, such as brivudine, idoxuridine, and ganciclovir. Viruses resistant because of altered substrate specificity of thymidine kinase may display cross-resistance to brivudine; those with altered DNA polymerase sensitivity may be resistant to brivudine and vidarabine. However, those viruses with altered enzyme specificity or sensitivity tend to have variable cross-resistance patterns and may be relatively susceptible to the aforementioned antivirals.

◊ References.

1. Bacon TH, *et al.* Herpes simplex virus resistance to acyclovir and penciclovir after two decades of antiviral therapy. *Clin Microbiol Rev* 2003; **16:** 114–28.
2. Malvy D, *et al.* A retrospective, case-control study of acyclovir resistance in herpes simplex virus. *Clin Infect Dis* 2005; **41:** 320–6.

Pharmacokinetics

Aciclovir is poorly absorbed from the gastrointestinal tract after oral doses. Bioavailability of oral aciclovir is

about 10 to 20%; orally active prodrugs such as valaciclovir (p.911) have been developed to overcome this poor absorption.

After intravenous dosage as aciclovir sodium it is widely distributed to body tissues and fluids including the CSF where concentrations achieved are about 50% of those achieved in plasma. Protein binding is reported to range from 9 to 33%.

Aciclovir is excreted largely unchanged in the urine, by glomerular filtration and some active tubular secretion, with up to 14% appearing in the urine as the inactive metabolite 9-carboxymethoxymethylguanine. In patients with normal renal function, the half-life is about 2 to 3 hours. In patients with chronic renal failure, this value is increased and may be up to 19.5 hours in anuric patients. During haemodialysis the half-life has been reported to be reduced to 5.7 hours, with 60% of a dose of aciclovir being removed. Faecal excretion may account for about 2% of a dose.

Probenecid increases the half-life and the area under the plasma concentration-time curve of aciclovir.

Aciclovir crosses the placenta and is distributed into breast milk in concentrations about 3 times higher than those in maternal serum.

Absorption of aciclovir is usually slight after topical application to intact skin, although it may be increased by changes in formulation. Aciclovir is absorbed after application of a 3% ointment to the eye giving a relatively high concentration in the aqueous humour but negligible amounts in the blood.

◊ Reviews.

1. de Miranda P, Blum MR. Pharmacokinetics of acyclovir after intravenous and oral administration. *J Antimicrob Chemother* 1983; **12** (suppl B): 29–37.
2. Laskin OL. Clinical pharmacokinetics of acyclovir. *Clin Pharmacokinet* 1983; **8:** 187–201.
3. Wagstaff AJ, *et al*. Aciclovir: a reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; **47:** 153–205.

Distribution. The pharmacokinetics of oral aciclovir and its distribution into the eye.[1]

1. Hung SO, *et al*. Pharmacokinetics of oral acyclovir (Zovirax) in the eye. *Br J Ophthalmol* 1984; **68:** 192–5.

Uses and Administration

Aciclovir is a synthetic purine nucleoside analogue structurally related to guanine. It is used mainly for the treatment and prophylaxis of viral infections due to herpes simplex virus types 1 and 2 (p.854) and varicella-zoster virus (herpes zoster and chickenpox—p.855).

Herpes simplex infections, including herpes keratitis, herpes labialis, and genital herpes, respond to aciclovir by the intravenous, oral, or topical route, given as soon as possible after symptoms appear. Both initial and recurrent infections can be successfully treated. Prolonged treatment can reduce the incidence of recurrence which is particularly important in immunocompromised patients. However, when prolonged treatment is withdrawn, infections may recur.

Aciclovir also improves the healing of herpes zoster lesions and reduces acute pain when given intravenously or by mouth; use to prevent postherpetic neuralgia is controversial (see p.9). Beneficial effects may be more marked in immunocompromised patients.

Aciclovir is given by ***intravenous infusion*** as the sodium salt over 1 hour. Doses are expressed in terms of the base. Aciclovir sodium 1.1 g is equivalent to about 1 g of aciclovir. Solutions for infusion are usually prepared to give a concentration of aciclovir of 25 or 50 mg/mL; this must then be further diluted to a final concentration not greater than about 5 mg/mL (0.5%). Alternatively, a solution containing 25 mg/mL may be given by injection using a controlled-rate infusion pump, over 1 hour. In obese patients the dose should be calculated on the basis of ideal body-weight, to avoid overdosage.

For **herpes simplex infections** in the *immunocompromised*, and for severe initial *genital herpes*, or for *prophylaxis* of herpes simplex infections in *immunocompromised* patients the dose by the intravenous route is 5 mg/kg given every 8 hours, and recommended periods of treatment range from 5 to 7 days. A higher dose of 10 mg/kg every 8 hours is given in the treatment of *herpes simplex encephalitis*, and treatment is usually continued for 10 days.

For **varicella-zoster infections** in immunocompetent patients, a dose of 5 mg/kg every 8 hours may also be given. In *immunocompromised* patients the higher dose of 10 mg/kg every 8 hours should be used.

Oral doses of aciclovir also vary according to indication. In **herpes simplex infections**:

- for treatment of *primary infections*, including genital herpes, the usual oral dose is 200 mg five times daily (usually every 4 hours while awake) for 5 to 10 days
- severely *immunocompromised* patients or those with *impaired absorption* may be given 400 mg five times daily for 5 days
- for *suppression* of recurrent herpes simplex in *immunocompetent* patients, the oral dose is 800 mg daily in two to four divided doses; dosage reduction to 400 to 600 mg daily can be tried. Higher doses of 1 g daily have also been used. Therapy should be interrupted every 6 to 12 months for reassessment of the condition

  Chronic suppressive treatment is not suitable for mild or infrequent recurrences of herpes simplex. In such cases *episodic treatment* of recurrences may be preferred; a dose of 200 mg five times daily for 5 days has been recommended, preferably begun during the prodromal period.
- for *prophylaxis* of herpes simplex in *immunocompromised* patients, the dose is 200 to 400 mg four times daily.

The usual oral dose of aciclovir for treatment of **chickenpox** is 800 mg four or five times daily for 5 to 7 days; for herpes zoster 800 mg five times daily may be given for 7 to 10 days.

In **herpes simplex infections of the skin**, including genital herpes and herpes labialis, ***topical treatment*** with an ointment or cream containing aciclovir 5% may be applied 5 or 6 times daily for periods of 5 to 10 days, preferably beginning in the prodromal period as soon as signs or symptoms occur. In herpes simplex **keratitis** a 3% eye ointment may be applied 5 times daily until 3 days after healing.

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

For details of doses in children, see Administration in Children, below.

◊ Reviews.

1. Wagstaff AJ, *et al*. Aciclovir: a reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; **47:** 153–205.
2. Leflore S, *et al.* A risk-benefit evaluation of aciclovir for the treatment and prophylaxis of herpes simplex virus infections. *Drug Safety* 2000; **23:** 131–42.

Administration in children. Aciclovir is licensed for use in infants and children for the treatment of herpes simplex and varicella-zoster infections, and for the prophylaxis of herpes simplex infections in the immunocompromised. It may be given by slow intravenous infusion over 1 hour, or orally.

Recommended ***intravenous doses*** vary according to country and age of the patient.

In the *UK* the 8-hourly dose for children aged 3 months to 12 years is calculated by body-surface. The usual course of treatment is 5 to 10 days:

- herpes simplex and varicella-zoster infections in immunocompetent patients: 250 mg/m^2
- varicella-zoster infection in immunocompromised children or those with herpes simplex encephalitis: 500 mg/m^2

In the *USA*, the 8-hourly intravenous dose for children aged 3 months to 12 years is calculated by body-weight:

- herpes simplex infections: 10 mg/kg for 7 days
- varicella-zoster infections in immunocompromised children: 20 mg/kg for 7 days
- herpes simplex encephalitis: 20 mg/kg for 10 days

In the *UK* and the *USA* the intravenous dose for neonates and infants up to 3 months of age is calculated by body-weight; an 8-hourly intravenous dose of 10 mg/kg may be given for the treatment of herpes simplex infections. Treatment for neonatal herpes simplex usually continues for 7 or 10 days. Higher intravenous doses of up to 20 mg/kg for at least 7 days have been recommended by the *BNFC* in neonates with varicella-zoster infections. A similar dose given for 14 days (21 days if CNS involvement) is also recommended in the treatment of disseminated herpes simplex in neonates and infants up to 3 months of age.

In the *UK* the following ***oral doses*** are permitted in the treatment of herpes simplex infections, and in the prophylaxis of herpes simplex infections in the immunocompromised:

- 2 years and over: usual adult dose (see above)
- under 2 years: half usual adult dose

In the *UK* and the *USA* the oral doses for the treatment of chickenpox are:

- over 2 years: 20 mg/kg, up to a maximum of 800 mg, four times daily for 5 days

Alternatively, the following oral doses may be used:

- under 2 years: 200 mg four times daily
- 2 to 5 years: 400 mg four times daily
- 6 years and over: 800 mg four times daily

Administration in renal impairment. Doses of aciclovir should be reduced in renal impairment according to creatinine clearance (CC) and licensed product information gives the following guidance:

intravenous dosage:

- CC between 25 and 50 mL/minute: the interval between infusions may be increased to 12 hours
- CC 10 to 25 mL/minute: the interval between infusions may be increased to 24 hours
- CC less than 10 mL/minute: patients on *peritoneal dialysis* should receive half the usual appropriate dose given once every 24 hours; patients on *haemodialysis* should receive half the usual dose every 24 hours plus an extra half-dose after haemodialysis

oral dosage:

- CC less than 10 mL/minute: *herpes simplex infections*: 200 mg every 12 hours; *varicella-zoster infections*: 800 mg every 12 hours
- CC between 10 and 25 mL/minute: *varicella-zoster infections*: 800 mg three times daily every 8 hours

Erythema multiforme. For patients with recurrent erythema multiforme (p.1580) associated with herpes simplex infection a 5-day course of oral aciclovir at the start of the infection has been proposed to prevent the subsequent skin lesions.[1] If this fails, a 6-month course of oral aciclovir has been found to be of benefit,[2] even if the association with herpes is not obvious. It should be noted, however, that erythema multiforme may occur as an adverse effect of systemic aciclovir.

1. Schofield JK, *et al*. Recurrent erythema multiforme: clinical features and treatment in a large series of patients. *Br J Dermatol* 1993; **128:** 542–5.
2. Tatnall FM, *et al*. A double-blind, placebo-controlled trial of continuous acyclovir therapy in recurrent erythema multiforme. *Br J Dermatol* 1995; **132:** 267–70.

Preparations

BP 2008: Aciclovir Cream; Aciclovir Eye Ointment; Aciclovir Intravenous Infusion; Aciclovir Oral Suspension; Aciclovir Tablets; Dispersible Aciclovir Tablets;
USP 31: Acyclovir Capsules; Acyclovir for Injection; Acyclovir Ointment; Acyclovir Oral Suspension; Acyclovir Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Acerpes; Aciclo; Aciclotex; Apofarm; Dioxis; Lafevir; Lisovyr; Poviral; Virostatic; Xiclovir; Zovirax; ***Austral.:*** Acihexal; Acyclo-V; Chemists Own Cold Sore; Lovir; Ozvir; Zolaten†; Zovirax; Zyclir; ***Austria:*** Acic; Aciclobene; Aciclostad; Aciclotyrol†; Activir; Acyclox; Exviral; Farocid†; Fibral; Herpomed; Nycovir; Simplex-Fieberblasen; Stadovir; ViroMed; Xorox; Zovirax; ***Belg.:*** Aciclomed; Aciclophar; Docaciclo; Viratop; Zovirax; ***Braz.:*** Aciclomed; Aiclor†; Aciclovan†; Aciveral; Acivirax; Anclomax; Antivirax; Aviral; Ciclavix†; Ciclocris†; Clovir; Ductovirax; Exavir†; Ezopen; Heclivir; Herpesil†; Hervirax; Hpvir; Uni Vir; Ziclovir†; Zovirax; Zoylex†; ***Canad.:*** Avirax†; Zovirax; ***Chile:*** Eurovir; Lisovyr; Oftavir; Vironida; Zovirax; ***Cz.:*** Acyclostad; Herpesin; Herpotern†; Provirsan; Ranvir; Supraviran†; Viro†; Virolex; Xorox†; Zovirax; ***Denm.:*** Aciclodan; Acivir; Avirox; Geavir; Herpavir; Orivir†; Zovir; ***Fin.:*** Aclovir; Acyclostad†; Acyrax; Antix; Geavir†; Herpolips; Zovirax; ***Fr.:*** Aciclovivax; Activir; Kendix; Virucalm; Zovirax; ***Ger.:*** Acerpes; Acic; Acic-Ophtal; Aciclo; Aciclobeta; Aciclostad; Acivir; Dynexan Herpescreme; Herpetad; Juviral†; Mapox†; Supraviran; Virax†; Virupos; Viruseen†; Virzin; Zoliparin; Zovirax; ***Gr.:*** Abduce; Biozirox; Cargosil; Cevinolon; Clovirax; Cyclovir†; Cycloviran; Erpaclovir; Erpizon; Etasisen; Hagevir; Helposol; Herzkur; Neldim; Pulibex; Uniplex†; Verpir; Virusteril; Xorox†; Zeramil; Zidovimm; Zovirax; ***Hong Kong:*** Acilax; Aclovirax; Acyvir; Avorax; Cusiviral; Cycloraz†; Cyclovax; Entir; Euroclovir; Lovir; Medovir; Qualiclovir; Synclovir; Vidaclovir; Virest; Viroclear; Virucid; Wariviron; Zevin; Zoral; Zoraxin; Zovirax; ***Hung.:*** Acyclostad; Herpesin; Telviran; Virokill†; Virolex; Zovirax; ***India:*** Acivir; Cyclovir; Herpex; Ocurax; Zovirax; ***Indon.:*** Acifar; Azovir; Clinovir; Clopes; Danovir; Herax; Herpiclof; Kenrovir; Matrovir; Molavir; Nevirz; Quavir; Scanovir; Viralis; Vircella; Vircovir; Virdam; Vireth; Virpes; Virtaz-200; Virules; Zorel; Zoter; Zovirax; Zumasid; Zyclorax; ***Irl.:*** Acic; Soothelip†; Viralief; Zovirax; ***Israel:*** Acivir; Acyclo-V; Cyclomed; Supra-Vir; Zovirax; ***Ital.:*** Aciclin; ACY; Acyvir; Alovir; Amodivyr; Avirase; Avix; Avyclor; Avyplus; Avysal†; Cevirin†; Citvir; Cycloviran; Dravyr; Efriviral; Esavir; Euclivir; Fuviron; Herpesnil; Iliaclor; Immunovir; Ipaviran; Ipsovir; Neclovir†; Neviran; Rexan; Riduvir; Sanavir; Sifiviral†; Voraclor; Zovirax; ***Jpn:*** Zovirax; ***Malaysia:*** Acylete; Avorax; Cusiviral; Cyclovax†; Declovir; Hepirax; Lovir; Medovir; Vacrax; Virest†; Virless; Zevin; Zoral; Zorax†; Zovirax; ***Mex.:*** Acifur; Akevir; Apo-Vir; Avirex-T; Bioviraz; Brimex; Cicloferon; Clirbest; Clociver; Clovex; Clyvorax; Epsin; Erser; Exaliver†; Firex; Hercivir; Herpilem; Isavir; Jersin; Kerastil; Laciken; Lesaclor; Maclov; Opthavir; Pharcilex†; Seracic; Sinarden; Sophivir; Soviclor; Vicloran; Viclovir; Virestat; Viroxil; Zetavir†; Zirconia; Ziverone; Zovirax; ***Neth.:*** Herpolips; Kruidvat Koortslipcreme; Zovirax; ***Norw.:*** Zovirax; ***NZ:*** Acicvir†; Lovir; Viraban; Zolaten; Zovirax; ***Philipp.:*** Acyhex; Cyclostad; Herpex; Klozivex; Virest; Zovirax; ***Pol.:*** Abbovir; Acix; Antivir; Awirol; Cusiviral; Hascovir; Herpesin; Herpex; Heviran; Virolex; Xorovir; Zovirax; ***Port.:*** Aciclosina; Aciclovax; Cicloviral; Divicil; Faulviral; Hermix-Sofex; Hermocil†; Herpex; Milavir; Vidovir; Zov800; Zovirax; ***Rus.:*** Aciclostad

(Ациклостад)†; Cyclovir (Цикловир); Herpesin (Герпесин); Lovir (Ловир); Medovir (Медовир); Virolex (Виролекс); Vivorax (Виворакс); Zovirax (Зовиракс); ***S.Afr.:*** Acitab DT; Acitop; Activir; Cyclivex; Lovire; Vyrohexal; Zovirax; ***Singapore:*** Avorax; Bearax; Cusiviral; Danovir†; Dravyr; Entir; Erlvirax†; Lovir; Medovir; Vacrax; Virest; Virless; Zoral; Zorax; Zovirax; ***Spain:*** Aciclostad; Bel Labial; Maynar; Milavir; Virherpes; Virmen; Viruderm; Zovirax; ***Swed.:*** Anti; Geavir; Zovirax; ***Switz.:*** Acerpes†; Acivir; Aviral; Helvevir; Virucalm; Zovirax; ***Thai.:*** ACV; Acyvir; Clinovir; Clovin; Clovira; Colsor; Cyclorax; Entir; Herpenon; Herpirax; Lermex; Marvir; Norum; Ranvir; Vermis; Vilerm; Viraxy; Virogon; Virolan; Viromed; Viropox†; Vivax; Vivir; Zevin; Zocovin; Zovirax; ***Turk.:*** Acyl; Aklovir; Asiviral; Hernovir; Herpeks; Klovireks-L; Provir; Silovir; Virosil; Virupos; Xorox; Zovirax; ***UAE:*** Lovrak; ***UK:*** Aviral; Clearsore; Herpetad; Soothelip; Virasorb; Virovir; Zovirax; ***USA:*** Zovirax; ***Venez.:*** Aciclor; Avir; Clorvil; Clovirex†; Herpiclor†; Herpin; Klovir†; Zovirax.

Adefovir *(BAN, USAN, rINN)*

Adéfovir; Adefovirum; GS-0393; PMEA. {[2-(6-Amino-9*H*-purin-9-yl)ethoxy]methyl}phosphonic acid; 9-[2-(Phosphonomethoxy)ethyl]adenine.

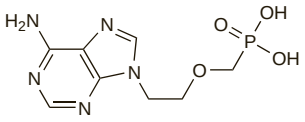
Адефовир

$C_8H_{12}N_5O_4P$ = 273.2.

CAS — 106941-25-7.

ATC — J05AF08.

ATC Vet — QJ05AF08.



Adefovir Dipivoxil *(BANM, USAN, rINNM)*

Adefovir Dipivoksil; Adéfovir Dipivoxil; Adefovirum Dipivoxilum; Dipivoxilo de adefovir; GS-0840; Piv2PMEA; *Bis*(POM)PMEA. 9-[2-({Bis[(pivaloyloxy)methoxy]phosphinyl}methoxy)ethyl]adenine.

Адефовир Дипивоксил

$C_{20}H_{32}N_5O_8P$ = 501.5.

CAS — 142340-99-6.

ATC — J05AF08.

ATC Vet — QJ05AF08.

Adverse Effects

The most common adverse effects reported from adefovir have been gastrointestinal effects including nausea, flatulence, diarrhoea, dyspepsia, and abdominal pain. Other common adverse effects are headache and asthenia. There have also been reports of pruritus and skin rashes. Increases in serum-creatinine concentrations may occur and there have been instances of renal impairment and acute renal failure; proximal renal tubulopathy, Fanconi syndrome, and hypophosphataemia have also been reported. Raised liver enzyme concentrations may occur and severe acute exacerbation of hepatitis has been reported after stopping treatment with adefovir.

Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with nucleoside analogues alone or with antiretrovirals (see Zidovudine, p.914).

Precautions

Adefovir should be withdrawn if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. Adefovir should be given with caution to patients with hepatomegaly or other risk factors for liver disease. Careful differentiation should be made between patients whose liver enzyme concentrations become elevated due to response to treatment and those in whom it is indicative of toxicity. Exacerbation of hepatitis has been reported in patients who developed resistance to adefovir and in those who stopped adefovir; patients who stop treatment should be monitored closely for an appropriate period. In order to minimise the risk of resistance in patients with lamivudine-resistant hepatitis B, adefovir should be used with lamivudine and not as monotherapy. Patients taking adefovir should be monitored every 3 months for signs of deteriorating renal function; particular care should be exercised in patients with a creatinine clearance of less than 50 mL/minute, who may require dosage modification, and in those receiving other drugs that may affect renal function.

Use of adefovir to treat chronic hepatitis B infection in patients with undiagnosed or untreated HIV infection may result in the emergence of resistant strains of HIV. US licensed product information recommends that all patients be tested for HIV antibodies before starting treatment with adefovir.

Breast feeding. It is not known whether adefovir is distributed into breast milk but licensed product information recommends that mothers should not breast feed if taking adefovir.

Pregnancy. Studies in *rodents* given high intravenous doses of adefovir (systemic exposure 38 times that in the human) have found it to be fetotoxic or embryotoxic; those given high oral doses (systemic exposure 23 to 40 times that in the human) or lower intravenous doses (systemic exposure 12 times that in the human) did not show evidence of teratogenicity or embryotoxicity. There are no studies available on the use of adefovir in pregnant women and licensed product information recommends that it should only be given to pregnant women if the potential benefit justifies the potential risk.

Interactions

Caution should be exercised when adefovir is given with other drugs eliminated by active tubular secretion as competition for the elimination pathway may increase the serum concentrations of either drug. Care is required when adefovir is given with other drugs with the potential for nephrotoxicity.

Antiviral Action

Adefovir is converted intracellularly in stages to the diphosphate, which then inhibits the DNA synthesis of hepatitis B virus through competitive inhibition of reverse transcriptase and incorporation into viral DNA. At high doses it has some activity against HIV.

Antiviral resistance. The development of antiviral resistance is a concern with long-term nucleoside or nucleotide treatment for chronic hepatitis B. Studies[1-4] in patients with chronic hepatitis B showed no resistance to adefovir after 1 year of treatment, but resistance rates increased over time to about 11%, 18%, and 29% at year 3, 4, and 5 respectively. Adefovir was found to be effective in patients who had previously developed resistance to lamivudine.[4]

1. Marcellin P, *et al.* Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med* 2003; **348:** 808–16. Correction. *ibid.*: 1192.
2. Hadziyannis SJ, *et al.* Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med* 2003; **348:** 800–7. Correction. *ibid.*; 1192.
3. Hadziyannis SJ, *et al.* Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. *N Engl J Med* 2005; **352:** 2673–81.
4. Delaney WE. Progress in the treatment of chronic hepatitis B: long-term experience with adefovir dipivoxil. *J Antimicrob Chemother* 2007; **59:** 827–32.

Pharmacokinetics

After oral doses adefovir dipivoxil is rapidly converted to adefovir. Peak plasma concentrations of adefovir occur after about 0.6 to 4 hours. Bioavailability is reported to be 59% after a single oral dose. Absorption is delayed but not reduced when given with food. Adefovir is widely distributed to body tissues, particularly into the kidneys, liver, and intestines. Less than 4% is bound to plasma or serum proteins. Adefovir is excreted renally by glomerular filtration and active tubular secretion; the terminal elimination half-life is reported to be about 7 hours. Adefovir is partially removed by haemodialysis.

Uses and Administration

Adefovir is a nucleotide reverse transcriptase inhibitor, structurally related to adenine, that is given orally as the prodrug adefovir dipivoxil for the treatment of chronic **hepatitis B** (p.851). It is used in adults with decompensated liver disease, or with compensated liver disease with evidence of active viral replication, persistently raised serum alanine aminotransferase concentrations, and histological evidence of active liver inflammation and fibrosis. The usual dose of adefovir dipivoxil is 10 mg once daily. For details of dosage modification in patients with renal impairment, see below.

Adefovir was initially investigated for the treatment of **HIV infection**, but its use is limited by nephrotoxicity due to the high doses needed.

◊ References.

1. Dando TM, Plosker GL. Adefovir dipivoxil: a review of its use in chronic hepatitis B. *Drugs* 2003; **63:** 2215–34.
2. Rivkin AM. Adefovir dipivoxil in the treatment of chronic hepatitis B. *Ann Pharmacother* 2004; **38:** 625–33.
3. Danta M, Dusheiko G. Adefovir dipivoxil: review of a novel acyclic nucleoside analogue. *Int J Clin Pract* 2004; **58:** 877–86.

Administration in renal impairment. The dosage of adefovir dipivoxil should be reduced in patients with renal impairment. The dosing interval should be modified according to the creatinine clearance (CC) of the patient:

- CC 50 mL or more per minute: usual 10 mg once-daily dosage (above)
- CC 30 to 49 mL/minute: 10 mg every 48 hours
- CC 10 to 29 mL/minute: 10 mg every 72 hours
- haemodialysis patients: 10 mg every 7 days after dialysis

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Biovir; Hepsera; ***Austral.:*** Hepsera; ***Belg.:*** Hepsera; ***Chile:*** Hepsera; ***Cz.:*** Hepsera; ***Denm.:*** Hepsera; ***Fin.:*** Hepsera; ***Ger.:*** Hepsera; ***Gr.:*** Hepsera; ***Hong Kong:*** Hepsera; ***Hung.:*** Hepsera; ***India:*** Adesera; ***Indon.:*** Hepsera; ***Irl.:*** Hepsera; ***Israel:*** Hepsera; ***Ital.:*** Hepsera; ***Malaysia:*** Hepsera; ***Mex.:*** Hepsera; ***Neth.:*** Hepsera; ***Norw.:*** Hepsera; ***NZ:*** Hepsera; ***Philipp.:*** Hepsera; ***Pol.:*** Hepsera; ***Port.:*** Hepsera; ***Singapore:*** Hepsera; ***Spain:*** Hepsera; ***Swed.:*** Hepsera; ***Switz.:*** Hepsera; ***Thai.:*** Hepsera; ***Turk.:*** Hepsera; ***UK:*** Hepsera; ***USA:*** Hepsera; ***Venez.:*** Hepsera.

Multi-ingredient: ***Fr.:*** Hepsera.

Amprenavir *(BAN, USAN, rINN)*

Amprenaviiri; Amprénavir; Amprenavirum; KVX-478; VX-478; 141W94. (3*S*)-Tetrahydro-3-furyl{(*S*)-α-[(1*R*)-1-hydroxy-2-(*N*^{1}-isobutylsulfanilamido)ethyl]phenethyl}carbamate.

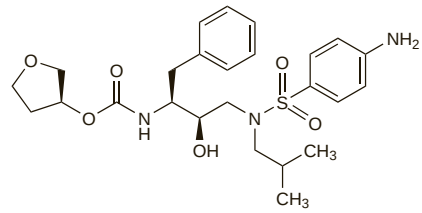
Ампренавир

$C_{25}H_{35}N_3O_6S$ = 505.6.

CAS — 161814-49-9.

ATC — J05AE05.

ATC Vet — QJ05AE05.



Adverse Effects

Adverse effects associated with antiretroviral regimens containing amprenavir are mostly mild to moderate. The most common adverse effects are gastrointestinal disturbances such as diarrhoea, flatulence, nausea, and vomiting. Other commonly reported adverse effects include fatigue, headache, oral paraesthesia, and taste disorders, while the most frequently reported serious adverse effects include peripheral paraesthesias, skin rash, and mood disorders (including depression). Mild to moderate rashes (usually erythematous or maculopapular and sometimes pruritic), generally occur during the second week of treatment and resolve within 2 weeks. A possible association with Stevens-Johnson syndrome has been reported with amprenavir.

Precautions

Amprenavir (when given with ritonavir) is contra-indicated in patients with severe hepatic impairment, and should be used with caution (and liver enzyme values monitored), in patients with mild to moderate liver disease. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors. Treatment with amprenavir should be permanently stopped in patients who develop a severe