(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.

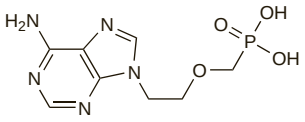
Адефовир

$C_8H_{12}N_5O_4P$ = 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.

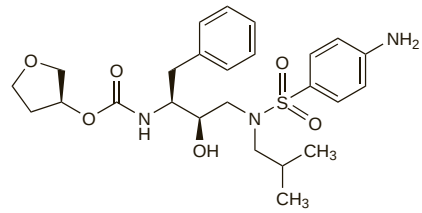
Ампренавир

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