(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.

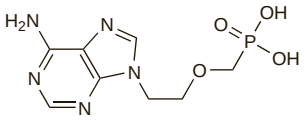
Адефовир

$C_8H_{12}N_5O_4P$ = 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.

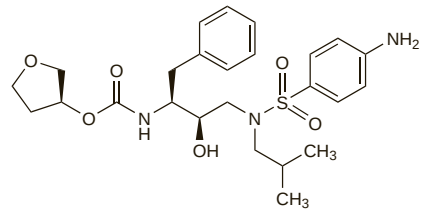
Ампренавир

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

or life-threatening skin rash or a skin rash with associated systemic or allergic symptoms or mucosal involvement.

Amprenavir is a sulfonamide and should be used with caution in patients known to be allergic to sulfonamides. The oral solution and capsule formulations (*Agenerase*, *GlaxoSmithKline*) also provide high daily doses of vitamin E (see p.1993). The oral solution has a high content of propylene glycol, present as an excipient, and appropriate precautions should be taken; it is contra-indicated in infants and young children, in pregnancy, and in hepatic or renal impairment. For further information on propylene glycol toxicity, see Adverse Effects and Precautions, p.2374.

Pregnancy. Amprenavir has been associated with teratogenicity in *animals*. The solution is contra-indicated in pregnancy due to the high propylene glycol content.

Interactions

Amprenavir is reported to be metabolised by the cytochrome P450 isoenzyme CYP3A4. It is also a modest inhibitor of the cytochrome P450 isoenzymes CYP3A4 and CYP2C19. Drugs that affect these isoenzymes may modify amprenavir plasma concentrations and amprenavir may alter the pharmacokinetics of other drugs that are metabolized by this enzyme system.

Amprenavir is contra-indicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include antiarrhythmics (amiodarone, bepridil, flecainide, propafenone, and quinidine), antihistamines (astemizole and terfenadine), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), sedatives and hypnotics (midazolam and triazolam) and statins (simvastatin and lovastatin). Rifampicin and St John's wort decrease the concentration of amprenavir; use with the antiretroviral is not recommended due to possible loss of its activity and development of resistance.

Agenerase oral solution (*GlaxoSmithKline*) is contra-indicated in patients taking disulfiram or other products that reduce alcohol metabolism (such as metronidazole) and in those taking alcohol-containing products (such as ritonavir oral solution) because of the potential risk of toxicity from its propylene glycol content.

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

Antiviral Action

Amprenavir is a selective, competitive, reversible inhibitor of HIV-1 and HIV-2 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Cross-resistance between HIV-protease inhibitors may occur, but cross-resistance between HIV-protease inhibitors and reverse transcriptase inhibitors is considered unlikely. Mechanisms of resistance to amprenavir may differ from those of other HIV-protease inhibitors.

Pharmacokinetics

Amprenavir is rapidly and well absorbed from the gastrointestinal tract after oral doses. Absorption is impaired by ingestion with a high-fat meal. Amprenavir capsules and oral solution are not bioequivalent; oral bioavailability is about 14% lower from the oral solution formulation than from the capsule formulation (*Agenerase*, *GlaxoSmithKline*). Peak plasma concentrations are attained 1 to 2 hours after a single dose. It is about 90% bound to plasma proteins. Amprenavir is metabolised by hepatic cytochrome P450 isoenzyme CYP3A4. It is excreted mainly in the faeces as metabolites. The plasma elimination half-life is 7.1 to 10.6 hours.

◊ References.

1. Sadler BM, Stein DS. Clinical pharmacology and pharmacokinetics of amprenavir. *Ann Pharmacother* 2002; **36:** 102–18.
2. Stein DS, *et al*. Pharmacokinetic and pharmacodynamic analysis of amprenavir-containing combination therapy in HIV-1-infected children. *J Clin Pharmacol* 2004; **44:** 1301–8.
3. Yogev R, *et al*. Single-dose safety and pharmacokinetics of amprenavir (141W94), a human immunodeficiency virus type 1 (HIV-1) protease inhibitor, in HIV-infected children. *Antimicrob Agents Chemother* 2005; **49:** 336–41.

Uses and Administration

Amprenavir is an HIV-protease inhibitor with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when amprenavir is used alone, and it is therefore used with other antiretrovirals.

Amprenavir is given orally as capsules or solution but the bioavailability of these formulations (*Agenerase*, *GlaxoSmithKline*) differ and their doses are not interchangeable.

- In adults and adolescents (13 to 16 years) weighing 50 kg or more the *capsules* are given in a dose of 1.2 g twice daily; when given with ritonavir (ritonavir-boosted amprenavir) the recommended dose is amprenavir 600 mg with ritonavir 100 mg twice daily or amprenavir 1.2 g with ritonavir 200 mg once daily.
- The *oral solution* is given in a dose of 17 mg/kg three times daily (maximum daily dose 2.8 g) or 1.4 g twice daily.

For details of doses in children and patients weighing less than 50 kg, see below. For dosage in hepatic impairment, also see below.

Amprenavir is also used in the form of the prodrug fosamprenavir (see p.877), which may aid compliance by reducing adverse effects and increasing flexibility of dosing.

◊ Reviews.

1. Noble S, Goa KL. Amprenavir: a review of its clinical potential in patients with HIV infection. *Drugs* 2000; **60:** 1383–1410.

Administration in children. For the treatment of HIV infection in children 4 to 12 years of age and in adolescents (13 to 16 years) weighing less than 50 kg, amprenavir is given daily with other antiretroviral drugs. Doses are based on body-weight:

- the *capsules* are given in an oral dose of 20 mg/kg twice daily or 15 mg/kg three times daily, to a maximum daily dose of 2.4 g, or
- the *solution* is given in an oral dose of 22.5 mg/kg twice daily or 17 mg/kg three times daily, to a maximum daily dose of 2.8 g

Administration in hepatic impairment. Amprenavir should be used with caution and in reduced doses in patients with hepatic impairment. Additionally, the oral solution contains propylene glycol and extra restrictions may apply.

The following doses have been recommended in UK licensed product information:

oral solution:

- do not use

capsules:

- moderate impairment: 450 mg twice daily
- severe impairment: 300 mg twice daily

The following doses have been recommended in US product information:

oral solution:

- Child-Pugh score 5 to 8: 513 mg twice daily
- Child-Pugh score 9 to 12: 342 mg twice daily
- hepatic failure: do not use

capsules:

- Child-Pugh score 5 to 8: 450 mg twice daily
- Child-Pugh score 9 to 12: 300 mg twice daily

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Agenerase; ***Austral.:*** Agenerase; ***Austria:*** Agenerase; ***Belg.:*** Agenerase†; ***Braz.:*** Agenerase; ***Canad.:*** Agenerase; ***Chile:*** Agenerase; ***Cz.:*** Agenerase; ***Denm.:*** Agenerase†; ***Fin.:*** Agenerase; ***Fr.:*** Agenerase; ***Ger.:*** Agenerase; ***Gr.:*** Agenerase; ***Irl.:*** Agenerase; ***Israel:*** Agenerase; ***Ital.:*** Agenerase; ***Mex.:*** Agenerase; ***Neth.:*** Agenerase; ***Norw.:*** Agenerase†; ***NZ:*** Agenerase; ***Pol.:*** Agenerase; ***Port.:*** Agenerase; ***Rus.:*** Agenerase (Агенераза); ***Spain:*** Agenerase; ***Swed.:*** Agenerase†; ***Switz.:*** Agenerase; ***Turk.:*** Agenerase; ***UK:*** Agenerase†; ***USA:*** Agenerase†; ***Venez.:*** Agenerase.

Atazanavir Sulfate *(USAN, rINNM)*

Atazanavir, Sulfate d'; Atazanavir Sulphate *(BANM)*; Atazanaviri Sulfas; BMS-232632-05; BMS-232632 (atazanavir); Sulfato de atazanavir. Dimethyl (3*S*,8*S*,9*S*,12*S*)-9-Benzyl-3,12-di-*tert*-butyl-8-hydroxy-4,11-dioxo-6-(*p*-2-pyridylbenzyl)-2,5,6,10,13-pentaazatetradecanedioate sulfate (1:1).

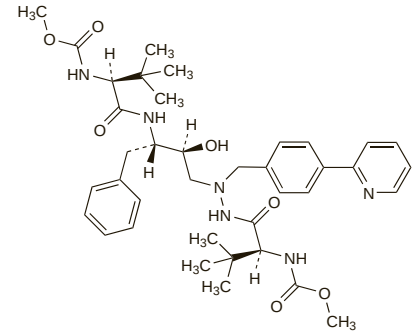
Атазанавира Сульфат

$C_{38}H_{52}N_6O_7,H_2SO_4$ = 802.9.

CAS — 198904-31-3 (atazanavir); 229975-97-7 (atazanavir sulfate).

ATC — J05AE08.

ATC Vet — QJ05AE08.



(atazanavir)

Adverse Effects

Commonly reported adverse effects of moderate or greater intensity associated with antiretroviral regimens containing atazanavir include gastrointestinal disturbances (abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, and jaundice), headache, insomnia, and peripheral neurological symptoms, and scleral icterus. Other commonly reported adverse effects are asthenia and fatigue. Mild to moderate rashes (usually maculopapular) generally occurring after 8 weeks of treatment and resolving within 1 to 2 weeks have been reported. Stevens-Johnson syndrome and erythema multiforme have also been reported in patients given atazanavir. Atazanavir may prolong the PR interval of the ECG and asymptomatic first-degree AV block has been reported in some patients. Cases of nephrolithiasis have occurred. Most patients taking atazanavir have asymptomatic elevations in unconjugated bilirubin, which is reversible upon stopping treatment. Other abnormal laboratory results include elevated amylase and lipase, elevated liver enzymes, and low neutrophils.

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 atazanavir, 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 seen in patients receiving antiretroviral therapy, including atazanavir. Metabolic abnormalities such as insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported; atazanavir does not appear to have a negative effect on lipid levels. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. 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 HIV-protease inhibitors see under Indinavir Sulfate, p.882.