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).

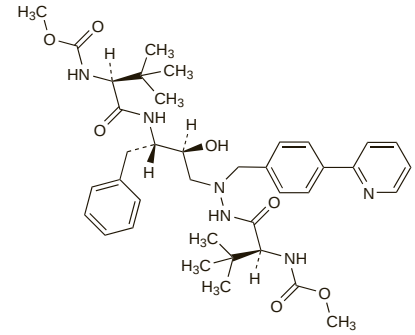
Атазанавира Сульфат

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

Precautions

Atazanavir is contra-indicated in patients with severe hepatic impairment and when given with ritonavir is also contra-indicated in more moderate hepatic impairment. It should be used with caution, and liver enzymes values monitored, in patients with mild 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. Caution should be exercised in patients with pre-existing cardiac conduction disorders or in those taking drugs that prolong the PR or increase the QT intervals. Patients developing jaundice or scleral icterus associated with hyperbilirubinaemia should be tried on an alternative antiretroviral; dose reductions of atazanavir should not be considered.

Pregnancy. Atazanavir has not been associated with teratogenicity in *animals*. It is not known whether atazanavir given to mothers will exacerbate physiologic hyperbilirubinaemia and lead to kernicterus in neonates and young infants.

Interactions

Atazanavir is extensively metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4 and inhibits CYP3A4, CYP2C8, and UGT1A1. Use with drugs primarily metabolised by these isoenzymes may result in increases in their plasma concentrations, while drugs that inhibit CYP3A4 may increase atazanavir plasma concentrations. When ritonavir-boosted atazanavir is given, the drug interaction profile for ritonavir may predominate because ritonavir is a more potent CYP3A4 inhibitor than atazanavir.

Atazanavir 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), antineoplastic (irinotecan), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), sedatives and hypnotics (midazolam, triazolam), and statins (simvastatin and lovastatin). Proton pump inhibitors, rifampicin, and St John's wort decrease the concentration of atazanavir; use with the antiretroviral is not recommended due to possible loss of its activity and development of resistance. Atazanavir should also not be given to patients taking indinavir, as indirect hyperbilirubinaemia may result. Atazanavir is also contra-indicated with irinotecan as azatanavir's inhibition of UGT1A1 may increase irinotecan toxicity.

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

Antiviral Action

Atazanavir is a selective, competitive, reversible inhibitor of HIV-1 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. Various degrees of cross-resistance between HIV-protease inhibitors may occur.

Pharmacokinetics

Atazanavir is rapidly absorbed from the gastrointestinal tract after oral doses with peak plasma concentrations occurring after 2 to 2.5 hours. On multiple dosing with a ritonavir-boosted regimen peak plasma concentrations are achieved after 3 hours. Bioavailability (of both ritonavir-boosted and non-boosted regimens) is enhanced if given with food. Atazanavir is reported to be 86% bound to serum proteins. It is distributed into semen and into the CSF. Atazanavir is extensively metabolised, mainly by oxidation by cytochrome P450 isoenzyme CYP3A; the metabolites appear to be inactive. Atazanavir is predominantly excreted in faeces, mainly as metabolites, and to a smaller extent in the urine. The terminal elimination half-life of atazanavir is reported to be about 7 hours and 8.6 hours after a ritonavir-boosted regimen.

◊ Reviews.

1. Le Tiec C, *et al.* Clinical pharmacokinetics and summary of efficacy and tolerability of atazanavir. *Clin Pharmacokinet* 2005; **44:** 1035–50.

Uses and Administration

Atazanavir is an HIV-protease inhibitor with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when atazanavir is used alone, and it is therefore used with other antiretrovirals.

Atazanavir is given orally as the sulfate with food, but doses are expressed in terms of atazanavir; 228 mg of atazanavir sulfate is equivalent to about 200 mg of atazanavir.

The usual adult dose in treatment-naive patients is 400 mg once daily. Ritonavir-boosted atazanavir (atazanavir 300 mg once daily with ritonavir 100 mg once daily) should be used when given with tenofovir, efavirenz, H_2-receptor antagonists, or proton pump inhibitors.

The usual dose in therapy-experienced patients is 300 mg once daily with ritonavir 100 mg once daily. A dose of atazanavir 400 mg once daily with ritonavir 100 mg once daily should be used when given with both tenofovir and an H_2-receptor antagonist.

For details of doses in children and adolescents, see below.

For details of recommended doses of atazanavir in patients with hepatic or renal impairment, see below.

◊ Reviews.

1. Havlir DV, O'Marro SD. Atazanavir: new option for treatment of HIV infection. *Clin Infect Dis* 2004; **38:** 1599–1604.
2. Musial BL, *et al.* Atazanavir: a new protease inhibitor to treat HIV infection. *Am J Health-Syst Pharm* 2004; **61:** 1365–74.
3. Orrick JJ, Steinhart CR. Atazanavir. *Ann Pharmacother* 2004; **38:** 1664–74.
4. Swainston Harrison T, Scott LJ. Atazanavir: a review of its use in the management of HIV infection. *Drugs* 2005; **65:** 2309–36.

Administration in children. For the treatment of HIV infection in children 6 years of age and older and adolescents, atazanavir is given orally with food. Doses are based on body-weight.

The recommended dosage of atazanavir with ritonavir in *treatment-naive* patients at least 6 years of age is:

- 15 to 24 kg: atazanavir 150 mg once daily with ritonavir 80 mg once daily
- 25 to 31 kg: atazanavir 200 mg once daily with ritonavir 100 mg once daily
- 32 to 38 kg: atazanavir 250 mg once daily with ritonavir 100 mg once daily
- 39 kg or more: atazanavir 300 mg once daily with ritonavir 100 mg once daily

For *treatment-naive* patients at least 13 years of age and 39 kg, who are unable to tolerate ritonavir, the recommended dose is atazanavir 400 mg once daily.

The recommended dosage of atazanavir with ritonavir in *treatment-experienced* patients at least 6 years of age is:

- 25 to 31 kg: atazanavir 200 mg once daily with ritonavir 100 mg once daily
- 32 to 38 kg: atazanavir 250 mg once daily with ritonavir 100 mg once daily
- 39 kg or more: atazanavir 300 mg once daily with ritonavir 100 mg once daily

Administration in hepatic impairment. In treatment-naive patients the oral dose of atazanavir should be adjusted in hepatic impairment as follows:

- mild hepatic impairment (Child-Pugh category A): use with caution (no specific reduction recommended)
- moderate impairment (Child-Pugh category B): atazanavir 300 mg daily
- severe hepatic impairment (Child-Pugh category C): not recommended

Ritonavir-boosted atazanavir regimens should be used with caution in patients with mild hepatic impairment and should not be used in those with moderate to severe hepatic impairment.

Administration in renal impairment. Oral dose adjustments are not usually necessary for patients with renal impairment. However, US licensed product information recommends that treatment-naive patients on haemodialysis should be given atazanavir 300 mg once daily with ritonavir 100 mg once daily and that atazanavir should not be used in treatment-experienced patients on haemodialysis.

Preparations

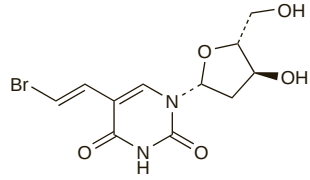
Proprietary Preparations (details are given in Part 3)
Arg.: Reyataz; ***Austral.:*** Reyataz; ***Belg.:*** Reyataz; ***Braz.:*** Reyataz; ***Canad.:*** Reyataz; ***Chile:*** Reyataz; ***Cz.:*** Reyataz; ***Denm.:*** Reyataz; ***Fin.:*** Reyataz; ***Fr.:*** Reyataz; ***Ger.:*** Reyataz; ***Gr.:*** Reyataz; ***Hong Kong:*** Reyataz; ***Hung.:*** Reyataz; ***Indon.:*** Reyataz; ***Irl.:*** Reyataz; ***Ital.:*** Reyataz; ***Jpn:*** Reyataz; ***Malaysia:*** Reyataz; ***Mex.:*** Reyataz; ***Neth.:*** Reyataz; ***Norw.:*** Reyataz; ***NZ:*** Reyataz; ***Pol.:*** Reyataz; ***Port.:*** Reyataz; ***Rus.:*** Reyataz (Реатаз); ***Singapore:*** Reyataz; ***Spain:*** Reyataz; ***Swed.:*** Reyataz; ***Switz.:*** Reyataz; ***Thai.:*** Reyataz; ***UK:*** Reyataz; ***USA:*** Reyataz.

Brivudine *(rINN)*

Brivudin; Brivudina; Brivudinum; BVDU. (*E*)-5-(2-Bromovinyl)-2′-deoxyuridine.

Бривудин

$C_{11}H_{13}BrN_2O_5$ = 333.1.
CAS — 69304-47-8.
ATC — J05AB15.
ATC Vet — QJ05AB15.



Profile

Brivudine is a nucleoside analogue effective *in vitro* against herpes simplex virus type 1 and varicella-zoster virus; other viruses including herpes simplex virus type 2 have been reported to be sensitive, but only at relatively high concentrations. The activity appears to be due, at least in part, to selective phosphorylation of brivudine by viral deoxythymidine kinase in preference to cellular kinases. There is the possibility of cross-resistance developing between brivudine and aciclovir because of some similar features in their mode of action (see p.863).

Brivudine is given orally in the treatment of herpes zoster (p.855) in a dose of 125 mg daily for 7 days. It has also been given orally for herpes simplex infection and has been used topically.

◊ References.

1. Keam SJ, *et al.* Brivudin (bromovinyl deoxyuridine). *Drugs* 2004; **64:** 2091–7.
2. Wassilew S. Collaborative Brivudin PHN Study Group. Brivudin compared with famciclovir in the treatment of herpes zoster: effects in acute disease and chronic pain in immunocompetent patients. A randomized, double-blind, multinational study. *J Eur Acad Dermatol Venereol* 2005; **19:** 47–55.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Zerpex; ***Cz.:*** Zostevir; ***Ger.:*** Zostex; ***Gr.:*** Brivir; Zostevir; ***Ital.:*** Brivirac; Zecovir; ***Port.:*** Bridic; Zostex; ***Spain:*** Brinix; Nervinex; Nervol; Zostydol†; ***Switz.:*** Brivex; ***Turk.:*** Zostex.

Cidofovir *(BAN, USAN, rINN)*

Cidofovirum; GS-504; GS-0504; HPMPC; Sidofoviiri; Sidofovir. {[(*S*)-2-(4-Amino-2-oxo-1(2*H*)-pyrimidinyl)-1-(hydroxymethyl)-ethoxy]methyl}phosphonic acid; 1-[(*S*)-3-Hydroxy-2-(phosphonomethoxy)propyl]-cytosine.

Цидофовир

$C_8H_{14}N_3O_6P$ = 279.2.
CAS — 113852-37-2 (anhydrous cidofovir); 149394-66-1 (cidofovir dihydrate).
ATC — J05AB12.
ATC Vet — QJ05AB12.