### 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

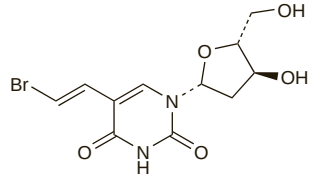
**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Reyataz; ***Austral.:*** Reyataz; ***Belg.:*** Reyataz; ***Braz.:*** Reyataz; ***Canad.:*** Reyataz; ***Chile:*** Reyataz; ***Cz.:*** Reyataz; ***Denm.:*** Reyataz; ***Fin.:*** Reyataz; ***Fr.:*** Reyataz; ***Ger.:*** Reyataz; ***Gr.:*** 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.*