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

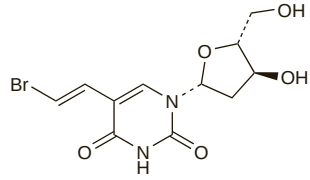
Proprietary Preparations (details are given in Part 3)
Arg.: Reyataz; ***Austral.:*** Reyataz; ***Belg.:*** Reyataz; ***Braz.:*** Reyataz; ***Canad.:*** Reyataz; ***Chile:*** Reyataz; ***Cz.:*** Reyataz; ***Denm.:*** Reyataz; ***Fin.:*** Reyataz; ***Fr.:*** Reyataz; ***Ger.:*** Reyataz; ***Gr.:*** Reyataz;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

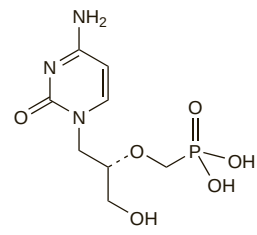
Proprietary Preparations (details are given in Part 3)
Belg.: Zerpex; ***Cz.:*** Zostevir; ***Ger.:*** Zostex; ***Gr.:*** Brivir; Zostevir; ***Ital.:*** Brivirac; Zecovir; ***Port.:*** Bridic; Zostex; ***Spain:*** Brinix; Nervinex; Nervol; Zostydol†; ***Switz.:*** Brivex; ***Turk.:*** Zostex.

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.



Adverse Effects

The most serious dose-limiting adverse effect of cidofovir is nephrotoxicity, the incidence and severity of which can be reduced by use with probenecid and by ensuring adequate hydration. There have been instances of acute renal failure after only 1 or 2 doses, and some fatalities. Low plasma-bicarbonate concentrations and metabolic acidosis, sometimes associated with proximal tubule injury and renal wasting syndrome (including Fanconi's syndrome) or with liver dysfunction and pancreatitis, have been reported. Reversible neutropenia has also occurred. Other adverse effects include nausea and vomiting, fever, asthenia, skin rash, dyspnoea, alopecia, and ocular hypotony (decreased intra-ocular pressure). Iritis or uveitis has been reported.

Cidofovir is carcinogenic and embryotoxic in *animals* and may have the potential to cause male infertility (see Precautions, below).

Effects on the eyes. Ocular adverse effects associated with intravenous use of cidofovir include iritis,[1] uveitis,[2-4] and ocular hypotony.[4] While development of ocular hypotony is considered to warrant withdrawal of cidofovir,[2] uveitis or iritis alone may respond to topical corticosteroids and cycloplegics thus allowing antiviral therapy to be continued; cidofovir must be stopped if there is no response or worsening of symptoms.

1. Tseng AL, *et al.* Iritis associated with intravenous cidofovir. *Ann Pharmacother* 1999; **33:** 167–71.
2. Ambati J, *et al.* Anterior uveitis associated with intravenous cidofovir use in patients with cytomegalovirus retinitis. *Br J Ophthalmol* 1999; **83:** 1153–8.
3. Rougier M-B, *et al.* Uvéite antérieure et cidofovir. *J Fr Ophtalmol* 2001; **24:** 491–5.
4. Rapp P, *et al.* Uvéite bilatérale et hypotonie définitive due au cidofovir intraveineux: à propos d'un cas. *J Fr Ophtalmol* 2003; **26:** 717–19.

Effects on the kidneys. Dose-related nephrotoxicity is the most severe adverse effect of cidofovir and marked proteinuria has been reported in up to 50% of patients. There have been instances of acute renal failure after only 1 or 2 doses, and some fatalities. Fanconi's syndrome associated with renal tubular damage has been reported in 2% of patients and, in one such patient, occurred on the third injection of cidofovir and resulted in irreversible renal impairment.[1] Reversible renal impairment with persisting Fanconi syndrome was reported in another.[2] A case of nephrogenic diabetes insipidus without premonitory laboratory abnormalities has also been reported in a patient given cidofovir.[3]

1. Vittecoq D, *et al.* Fanconi syndrome associated with cidofovir therapy. *Antimicrob Agents Chemother* 1997; **41:** 1846.
2. Kazory A, *et al.* Simultaneous development of Fanconi syndrome and acute renal failure associated with cidofovir. *J Antimicrob Chemother* 2007; **60:** 193–4.
3. Schliefer K, *et al.* Nephrogenic diabetes insipidus in a patient taking cidofovir. *Lancet* 1997; **350:** 413–14. Correction. *ibid.*; 1558.

Precautions

Cidofovir is contra-indicated in patients with renal impairment. Renal function should be measured before each dose. In the UK it is recommended that treatment should be interrupted or stopped if renal function deteriorates, but in the USA reduction of the dosage is permitted for increases in serum creatinine up to 300 to 400 micrograms/dL above baseline. Patients should receive oral probenecid and intravenous hydration with each dose of cidofovir. Neutrophil counts should also be monitored and regular ophthalmological follow-up is recommended. Patients with diabetes mellitus are at increased risk of ocular hypotony.

Cidofovir is carcinogenic and embryotoxic in *animals*. Cidofovir should not be given during pregnancy and both sexes should use effective methods of contraception during treatment; in addition, effective contraception should be used, for 1 month by women and for 3 months by men, after the end of treatment. There is also a possibility that cidofovir may cause male infertility.

Cidofovir should be given intravenously only; direct intra-ocular injection has been associated with significant ocular hypotony and visual impairment and is contra-indicated.

Interactions

Additive nephrotoxicity may occur if cidofovir is used with other nephrotoxic drugs such as aminoglycosides, amphotericin B, foscarnet, intravenous pentamidine, vancomycin, or NSAIDs. Potentially nephrotoxic drugs should be stopped at least 7 days before starting cidofovir. Probenecid, which is given with cidofovir, may alter the clearance of other drugs (see Interactions under Probenecid, p.558).

Patients with CMV retinitis are at increased risk of adverse inflammatory effects if cidofovir is given within 2 to 4 weeks of intravitreal fomivirsen.

Antiviral Action

Cidofovir undergoes intracellular phosphorylation by cellular kinases to the antiviral metabolite, cidofovir diphosphate, which acts as a competitive inhibitor of viral DNA polymerase. It is active against a range of herpesviruses including CMV, and, since its activity is not reliant on viral enzymes, may retain activity against some aciclovir- and foscarnet-resistant viruses. Cross-resistance with ganciclovir is common.

◊ References.

1. Cherrington JM, *et al.* In vitro antiviral susceptibilities of isolates from cytomegalovirus retinitis patients receiving first- or second-line cidofovir therapy: relationship to clinical outcome. *J Infect Dis* 1998; **178:** 1821–5.
2. Jabs DA, *et al.* Incidence of foscarnet resistance and cidofovir resistance in patients treated for cytomegalovirus retinitis. *Antimicrob Agents Chemother* 1998; **42:** 2240–4.

Pharmacokinetics

After intravenous doses of cidofovir, serum concentrations decline with a reported terminal half-life of about 2.2 hours (the intracellular half-life of the active diphosphate may be up to 65 hours). Cidofovir is eliminated mainly by renal excretion, both by glomerular filtration and tubular secretion. About 80 to 100% of a dose is recovered unchanged from the urine within 24 hours. Use with probenecid may reduce the excretion of cidofovir to some extent by blocking tubular secretion, although 70 to 85% has still been reported to be excreted unchanged in the urine within 24 hours.

◊ References.

1. Cundy KC. Clinical pharmacokinetics of the antiviral nucleotide analogues cidofovir and adefovir. *Clin Pharmacokinet* 1999; **36:** 127–43.
2. Brody SR, *et al.* Pharmacokinetics of cidofovir in renal insufficiency and in continuous ambulatory peritoneal dialysis or high-flux hemodialysis. *Clin Pharmacol Ther* 1999; **65:** 21–8.
3. Wolf DL, *et al.* Pharmacokinetics and renal effects of cidofovir with a reduced dose of probenecid in HIV-infected patients with cytomegalovirus retinitis. *J Clin Pharmacol* 2003; **43:** 43–51.

Uses and Administration

Cidofovir is a nucleoside analogue that is active against herpesviruses. It is used in the treatment of CMV retinitis (p.853) in patients with AIDS, and is being investigated for ocular herpes simplex and other viral infections.

In the treatment of CMV retinitis, cidofovir is given in a dose of 5 mg/kg by intravenous infusion over 1 hour once a week for 2 consecutive weeks, then once every 2 weeks for maintenance. Probenecid 2 g is given orally 3 hours before each dose of cidofovir and further 1-g doses of probenecid at 2 and 8 hours after completion of the infusion. To ensure adequate hydration, 1 litre of sodium chloride 0.9% is given by intravenous infusion over 1 to 2 hours immediately before each infusion of cidofovir; if the additional fluid load can be tolerated, a further 1 litre of sodium chloride 0.9% may be infused over 1 to 3 hours, starting at the same time as (or immediately after) the cidofovir infusion. For details of modified use of cidofovir in patients with renal impairment, see below.

Cidofovir has also been given experimentally by intravitreal injection but the commercially available formulation is unsuitable for use by this route and licensed product information advises against it (see Precautions, above).

An orally active prodrug of cidofovir known as cyclic-HPMPC (GS-930) is under investigation. Cidofovir has also been investigated for topical use.

◊ Reviews.

1. Lea AP, Bryson HM. Cidofovir. *Drugs* 1996; **52:** 225–30.
2. Kendle JB, Fan-Havard P. Cidofovir in the treatment of cytomegaloviral disease. *Ann Pharmacother* 1998; **32:** 1181–92.
3. Plosker GL, Noble S. Cidofovir: a review of its use in cytomegalovirus retinitis in patients with AIDS. *Drugs* 1999; **58:** 325–45.
4. De Clercq E. Cidofovir in the treatment of poxvirus infections. *Antiviral Res* 2002; **55:** 1–13.
5. Snoeck R, De Clercq E. Role of cidofovir in the treatment of DNA virus infections, other than CMV infections, in immunocompromised patients. *Curr Opin Investig Drugs* 2002; **3:** 1561–6.

Administration in renal impairment. Cidofovir is contra-indicated in patients with pre-existing renal impairment (serum creatinine more than 1.5 mg/dL) and should be interrupted or stopped if serum creatinine increases by more than 500 micrograms/dL during therapy; in the USA, a reduction in the maintenance dose from 5 to 3 mg/kg is permitted for increases of serum creatinine of up to 300 to 400 micrograms/dL above baseline.

Viral infections. In addition to its use in CMV retinitis, cidofovir has been studied in herpes simplex infections,[1-6] papillomavirus infections,[7-13] molluscum contagiosum,[11,14,15] and progressive multifocal leukoencephalopathy.[16-20]

1. Lalezari JP, *et al.* Treatment with intravenous (S)-1-[3-hydroxy-2-(phosphonylmethoxy)propyl]-cytosine of acyclovir-resistant mucocutaneous infection with herpes simplex virus in a patient with AIDS. *J Infect Dis* 1994; **170:** 570–2.
2. Lalezari J, *et al.* A randomized, double-blind, placebo-controlled trial of cidofovir gel for the treatment of acyclovir-unresponsive mucocutaneous herpes simplex virus infection in patients with AIDS. *J Infect Dis* 1997; **176:** 892–8.
3. Sacks SL, *et al.* A multicenter phase I/II dose escalation study of single-dose cidofovir gel for treatment of recurrent genital herpes. *Antimicrob Agents Chemother* 1998; **42:** 2996–9.
4. Bryant P, *et al.* Successful treatment of foscarnet-resistant herpes simplex stomatitis with intravenous cidofovir in a child. *Pediatr Infect Dis J* 2001; **20:** 1083–6.
5. Kopp T, *et al.* Successful treatment of an aciclovir-resistant herpes simplex type 2 infection with cidofovir in an AIDS patient. *Br J Dermatol* 2002; **147:** 134–8.
6. Andrei G, *et al.* Dual infection with polyomavirus BK and acyclovir-resistant herpes simplex virus successfully treated with cidofovir in a bone marrow transplant recipient. *Transpl Infect Dis* 2007; **9:** 126–31.
7. Snoeck R, *et al.* Treatment of anogenital papillomavirus infections with an acyclic nucleoside phosphonate analogue. *N Engl J Med* 1995; **333:** 943–4.
8. Davis MDP, *et al.* Large plantar wart caused by human papillomavirus-66 and resolution by topical cidofovir therapy. *J Am Acad Dermatol* 2000; **43:** 340–3.
9. Descamps V, *et al.* Topical cidofovir for bowenoid papulosis in an HIV-infected patient. *Br J Dermatol* 2001; **144:** 642–3.
10. Snoeck R, *et al.* Phase II double-blind, placebo-controlled study of the safety and efficacy of cidofovir topical gel for the treatment of patients with human papillomavirus infection. *Clin Infect Dis* 2001; **33:** 597–602.
11. Calista D. Topical cidofovir for severe cutaneous human papillomavirus and molluscum contagiosum infections in patients with HIV/AIDS: a pilot study. *J Eur Acad Dermatol Venereol* 2000; **14:** 484–8.
12. Husak R, *et al.* Refractory human papillomavirus-associated oral warts treated topically with 1-3% cidofovir solutions in human immunodeficiency virus type 1-infected patients. *Br J Dermatol* 2005; **152:** 590–1.
13. Kottke MD, Parker SRS. Intravenous cidofovir-induced resolution of disfiguring cutaneous human papillomavirus infection. *J Am Acad Dermatol* 2006; **55:** 533–6.
14. Davies EG, *et al.* Topical cidofovir for severe molluscum contagiosum. *Lancet* 1999; **353:** 2042.
15. Toro JR, *et al.* Topical cidofovir: a novel treatment for recalcitrant molluscum contagiosum in children infected with human immunodeficiency virus 1. *Arch Dermatol* 2000; **136:** 983–5.
16. Segarra-Newnham M, Vodolo KM. Use of cidofovir in progressive multifocal leukoencephalopathy. *Ann Pharmacother* 2001; **35:** 741–4.
17. Razonable RR, *et al.* Cidofovir treatment of progressive multifocal leukoencephalopathy in a patient receiving highly active antiretroviral therapy. *Mayo Clin Proc* 2001; **76:** 1171–5.
18. Marra CM, *et al.* Adult AIDS Clinical Trials Group 363 Team. A pilot study of cidofovir for progressive multifocal leukoencephalopathy in AIDS. *AIDS* 2002; **16:** 1791–7.
19. Garvey L, *et al.* Progressive multifocal leukoencephalopathy: prolonged survival in patients treated with protease inhibitors and cidofovir: a case series. *AIDS* 2006; **20:** 791–3.
20. Viallard JF, *et al.* Improvement of progressive multifocal leukoencephalopathy after cidofovir therapy in a patient with a destructive polyarthritis. *Infection* 2007; **35:** 33–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Vistide; ***Austria:*** Vistide; ***Belg.:*** Vistide; ***Cz.:*** Vistide; ***Fr.:*** Vistide; ***Ger.:*** Vistide; ***Gr.:*** Vistide†; ***Ital.:*** Vistide; ***Neth.:*** Vistide; ***Port.:*** Vistide; ***Spain:*** Vistide; ***Switz.:*** Vistide; ***UK:*** Vistide; ***USA:*** Vistide.

Darunavir *(USAN, rINN)*

Darunavirum; TMC-114; UIC-94017. (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-2-hydroxy-3-(*N*^{1}-isobutylsulfanilamido)propyl]carbamate.

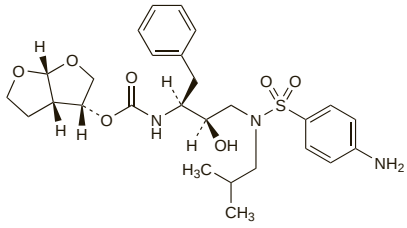
Дарунавир

$C_{27}H_{37}N_3O_7S$ = 547.7.

CAS — 206361-99-1.

ATC — J05AE10.

ATC Vet — QJ05AE10.



Darunavir Ethanolate *(rINNM)*

Darunavir monoethanolate.

$C_{27}H_{37}N_3O_7S,C_2H_5OH$ = 593.7.

ATC — J05AE10.

ATC Vet — QJ05AE10.

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing darunavir are gastrointestinal disturbances (abdominal pain, diarrhoea, nausea, and vomiting), nasopharyngitis, and hypertriglyceridaemia. Other reported adverse effects are asthenia, dizziness, fatigue, headache, and insomnia. Less frequently reported adverse effects include folliculitis, myocardial infarction, osteopenia, osteoporosis, polyuria, somnolence, tachycardia, transient ischaemic attacks, and vertigo. Severe cases of skin rashes have been reported, including erythema multiforme and Stevens-Johnson syndrome. Cases of drug-induced hepatitis, including fatalities, have been reported. Abnormal liver and pancreatic function tests and decreases in white blood cell counts have also occurred.

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 darunavir, 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 darunavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. 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

Patients should undergo liver function tests before starting and during treatment with darunavir. It should not be used in patients with severe hepatic impairment (Child-Pugh class C), and should be used with caution (and liver enzymes values monitored), in those with mild to moderate impairment (Child-Pugh A or B) and those with chronic hepatitis B or C co-infection. 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. All patients should be instructed to seek medical advice if symptoms suggestive of new or worsening hepatotoxicity occur. 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. An association with erythema multiforme and Stevens-Johnson syndrome has been reported and treatment should be stopped in patients who develop skin rashes.

Interactions

Darunavir is extensively metabolised by the cytochrome P450 isoenzyme CYP3A4. It may compete with other drugs metabolised by this enzyme, potentially resulting in increased plasma concentrations and toxicity.

Darunavir 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, quinidine, and systemic lidocaine), 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). Ritonavir-boosted lopinavir, rifampicin, antiepileptics (carbamazepine, phenobarbital, and phenytoin), and St John's wort decrease the concentration of darunavir; use with darunavir is not recommended due to the possible loss of its activity and development of resistance.

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

Antiviral Action

Darunavir is a selective 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. Cross-resistance may develop between some HIV-protease inhibitors, but mechanisms of resistance to darunavir may differ from those to other drugs of the class.

Pharmacokinetics

Darunavir is rapidly absorbed after oral doses, resulting in a bioavailability of 82% when taken with recommended doses of ritonavir; food increases the bioavailability. Peak plasma concentrations are reached within 2.5 to 4 hours. Darunavir is about 95% bound to plasma proteins. It is metabolised by oxidation by the cytochrome P450 system (primarily the isoenzyme CYP3A4), with at least 3 metabolites showing some antiretroviral activity. About 80% of a dose is excreted in the faeces, with 41.2% of this as unchanged drug; 14% is excreted in the urine, with 7.7% being unchanged drug. The mean terminal elimination half-life of darunavir is about 15 hours.

◊ Reviews.

1. Rittweger M, Arastéh K. Clinical pharmacokinetics of darunavir. *Clin Pharmacokinet* 2007; **46:** 739–56.

Uses and Administration

Darunavir 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 darunavir is used alone, and it is therefore used with other antiretrovirals.

Darunavir is boosted with low-dose ritonavir, which acts as a pharmacokinetic enhancer. It is given orally as the ethanolate, but doses are expressed in terms of the base; 325 mg of darunavir ethanolate is equivalent to about 300 mg of darunavir. The dose is 600 mg (with ritonavir 100 mg) twice daily with food.

◊ References.

1. Clotet B, *et al*. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. *Lancet* 2007; **369:** 1169–78.
2. Busse KH, Penzak SR. Darunavir: a second-generation protease inhibitor. *Am J Health-Syst Pharm* 2007; **64:** 1593–602.
3. Fenton C, Perry CM. Darunavir: in the treatment of HIV-1 infection. *Drugs* 2007; **67:** 2791–801.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Prezista; ***Cz.:*** Prezista; ***Gr.:*** Prezita; ***Port.:*** Prezista; ***UK:*** Prezista; ***USA:*** Prezista.

Delavirdine Mesilate *(rINNM)*

Délavirdine, Mésilate de; Delavirdine Mesylate *(USAN)*; Delavirdini Mesilas; Mesilato de delavirdina; U-90152S. 1-[3-(Isopropylamino)-2-pyridyl]-4-[(5-methanesulfonamidoindol-2-yl)carbonyl]-piperazine monomethanesulfonate.

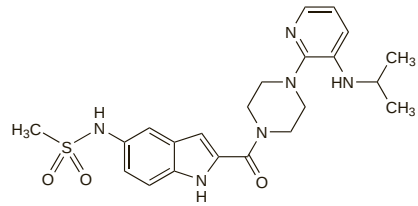
Делавирдина Мезилат

$C_{22}H_{28}N_6O_3S,CH_4O_3S$ = 552.7.

CAS — 136817-59-9 (delavirdine); 147221-93-0 (delavirdine mesilate).

ATC — J05AG02.

ATC Vet — QJ05AG02.



(delavirdine)

Adverse Effects

Adverse effects associated with antiretroviral regimens containing delavirdine are mostly mild to moderate. The most common adverse effect of delavirdine is skin rash, (usually diffuse, maculopapular, erythematous, and often pruritic), generally appearing within the first 3 weeks of starting therapy and resolving in 3 to 14 days. Severe skin reactions, including erythema multiforme and Stevens-Johnson syndrome, have occurred. Additional adverse effects of moderate to severe intensity include generalised abdominal pain, asthenia, fatigue, fever, flu syndrome, headache, and localised pain. Other reported adverse effects include gastrointestinal disturbances (diarrhoea, nausea, vomiting), increased liver enzyme values, anxiety, depressive symptoms, insomnia, and respiratory effects (bronchitis, cough, pharyngitis, sinusitis, and upper respiratory-tract infections). Liver failure, haemolytic anaemia, rhabdomyolysis, and acute renal failure have been reported during postmarketing use.

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 delavirdine, 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 delavirdine.

Precautions

Delavirdine should be stopped if a severe skin rash develops or if a rash is accompanied by fever, blistering, oral lesions, conjunctivitis, swelling, or muscle or joint aches. Delavirdine should be used with caution in patients with hepatic impairment.

Pregnancy. Delavirdine has been shown to be teratogenic in *animals*. Clinical studies and postmarketing data have identified 10 infants born to mothers who took delavirdine during pregnancy. Eight of the infants were born healthy, 1 infant was born HIV-