positive but had no congenital abnormalities, and 1 infant was born prematurely with a small muscular ventricular septal defect that spontaneously resolved.

Interactions

Delavirdine is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4. Consequently it may compete with other drugs metabolised by this system, potentially resulting in mutually increased plasma concentrations and toxicity. Alternatively, enzyme inducers may decrease plasma concentrations of delavirdine. The absorption of delavirdine is reduced by drugs that raise gastric pH such as antacids and histamine H_2-antagonists.

Delavirdine 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 antihistamines (astemizole and terfenadine), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), and sedatives and hypnotics (alprazolam, midazolam, triazolam). The antiepileptics carbamazepine, phenytoin, and phenobarbital, the antimycobacterials rifabutin and rifampicin, and St John's wort decrease the concentration of delavirdine; use with the antiretroviral is not recommended due to the possible loss of antiviral activity and development of resistance. For further information on drug interactions of NNRTIs see Table 2, p.944.

Antibacterials. Plasma concentrations of *dapsone* and *rifabutin* may be increased by delavirdine; *rifabutin* and *rifampicin*[1] may reduce delavirdine plasma concentrations and the use of either of these drugs with delavirdine is not recommended.

1. Borin MT, *et al.* Pharmacokinetic study of the interaction between rifampin and delavirdine mesylate. *Clin Pharmacol Ther* 1997; **61:** 544–53.

Antivirals. Use of delavirdine with buffered *didanosine* may result in reduced plasma concentrations of both drugs[1] and they should be given at least 1 hour apart; plasma concentrations of HIV-protease inhibitors including *indinavir* and *saquinavir* may be increased by delavirdine (see Antivirals, under Interactions of Indinavir, p.883) and liver function should be monitored in patients given delavirdine and saquinavir.

1. Morse GD, *et al.* Single-dose pharmacokinetics of delavirdine mesylate and didanosine in patients with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1997; **41:** 169–74.

Antiviral Action

Delavirdine acts by non-competitive inhibition of HIV-1 reverse transcriptase; it binds to the enzyme, disrupting the conformation of its catalytic site and impairing its RNA- and DNA-dependent polymerase activity.

Resistance to delavirdine and emergence of cross-resistance to other non-nucleoside reverse transcriptase inhibitors has been seen.

Pharmacokinetics

Delavirdine is rapidly absorbed after oral doses, peak plasma concentrations occurring after about 1 hour. The bioavailability of delavirdine tablets is about 85% of that from an oral solution after a single dose. The bioavailability of the 100-mg tablet can be increased by about 20% by dissolving it in water before use; the 200-mg tablets do not readily disperse in water and should be swallowed intact. Delavirdine is about 98% bound to plasma proteins. It is extensively metabolised by hepatic microsomal enzymes, principally by the cytochrome P450 isoenzyme CYP3A4 (although CYP2D6 may play some role), to several inactive metabolites. The plasma half-life after usual dosage is about 5.8 hours and ranges from 2 to 11 hours. Delavirdine is excreted as metabolites in the urine and faeces. Less than 5% is excreted in the urine unchanged.

◊ Reviews.

1. Voorman RL, *et al.* Metabolism of delavirdine, a human immunodeficiency virus type-1 reverse transcriptase inhibitor, by microsomal cytochrome P450 in humans, rats, and other species: probable involvement of CYP2D6 and CYP3A. *Drug Metab Dispos* 1998; **26:** 631–9.
2. Tran JQ, *et al.* Delavirdine: clinical pharmacokinetics and drug interactions. *Clin Pharmacokinet* 2001; **40:** 207–26.
3. Shelton MJ, *et al.* Pharmacokinetics of ritonavir and delavirdine in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 2003; **47:** 1694–9.
4. Smith PF, *et al.* Population pharmacokinetics of delavirdine and N-delavirdine in HIV-infected individuals. *Clin Pharmacokinet* 2005; **44:** 99–109.

Uses and Administration

Delavirdine is a non-nucleoside reverse transcriptase inhibitor with activity against HIV-1. Viral resistance emerges rapidly when delavirdine is used alone, and it is therefore used with other antiretrovirals for combination therapy of HIV infection and AIDS (p.856).

Delavirdine is given orally as the mesilate in a usual dose of 400 mg three times daily. Some tablet formulations may be dispersed in water before use in order to increase bioavailability (see above).

◊ Reviews.

1. Scott LJ, Perry CM. Delavirdine: a review of its use in HIV infection. *Drugs* 2000; **60:** 1411–44.

Preparations

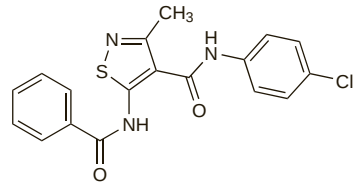
Proprietary Preparations (details are given in Part 3)
Austral.: Rescriptor; ***Canad.:*** Rescriptor; ***Mex.:*** Rescriptor†; ***USA:*** Rescriptor.

Denotivir *(pINN)*

Dénotivir; Denotivirum. 5-Benzamido-4′-chloro-3-methyl-4-isothiazolecarboxanilide.

Денотивир

$C_{18}H_{14}ClN_3O_2S$ = 371.8.
CAS — 51287-57-1.



Profile

Denotivir has antiviral, antibacterial, and anti-inflammatory properties. It is used topically as a 3% cream in the treatment of herpes virus infections and in other skin disorders complicated by bacterial infection.

Preparations

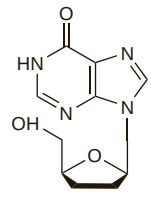
Proprietary Preparations (details are given in Part 3)
Pol.: Polvir; Vratizolin.

Didanosine *(BAN, USAN, rINN)*

BMY-40900; ddI; ddIno; Didanocin; Didanosiini; Didanosin; Didanosina; Didanosinum; Didanozin; Didanozinas; Dideoxyinosine; NSC-612049. 2′,3′-Dideoxyinosine.

Диданозин

$C_{10}H_{12}N_4O_3$ = 236.2.
CAS — 69655-05-6.
ATC — J05AF02.
ATC Vet — QJ05AF02.



Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*
Ph. Eur. 6.2 (Didanosine). A white or almost white, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol and in methyl alcohol; freely soluble in dimethyl sulfoxide.
USP 31 (Didanosine). A white to off-white crystalline powder. Practically insoluble or insoluble in acetone and in methyl alcohol; very soluble in dimethyl sulfoxide. Store at a temperature of 20° to 25°, excursions permitted between 15° and 30°.

Adverse Effects

The most common serious adverse effects of didanosine are peripheral neuropathy and potentially fatal pancreatitis. Other commonly reported adverse effects include abdominal pain, diarrhoea, fatigue, headache, nausea, rash, and vomiting. Abnormal liver function tests may occur and hepatitis or fatal hepatic failure has been reported rarely; fatalities were reported most often in patients taking didanosine with stavudine and hydroxycarbamide. Retinal and optic-nerve changes have been reported in children, particularly in those taking higher than recommended doses; retinal depigmentation has been reported in adult patients. Other adverse effects include alopecia, anaemia, asthenia, dry mouth, fever, flatulence, parotid gland enlargement, leucopenia, hypersensitivity reactions including anaphylaxis, hyperuricaemia, and thrombocytopenia. Lactic acidosis and severe hepatomegaly with steatosis, sometimes fatal, and generally occurring after some months of treatment has been reported.

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 didanosine, 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 didanosine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction such as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. For further information on adverse effects associated with NRTIs see Zidovudine, p.914.

Effects on the blood. In general, haematological abnormalities are less common in patients taking didanosine than in those taking zidovudine. However, there have been reports of thrombocytopenia associated with didanosine.[1-3]

1. Butler KM, *et al.* Dideoxyinosine in children with symptomatic human immunodeficiency virus infection. *N Engl J Med* 1991; **324:** 137–44.
2. Lor E, Liu YQ. Didanosine-associated eosinophilia with acute thrombocytopenia. *Ann Pharmacother* 1993; **27:** 23–5.
3. Herranz P, *et al.* Cutaneous vasculitis associated with didanosine. *Lancet* 1994; **344:** 680.

Effects on the eyes. Retinal lesions with atrophy of the retinal pigment epithelium at the periphery of the retina were reported in 4 children receiving didanosine doses of 270 to 540 mg/m^2 daily.[1]

1. Whitcup SM, *et al.* Retinal lesions in children treated with dideoxyinosine. *N Engl J Med* 1992; **326:** 1226–7.

Effects on the heart. For the possible risk of myocardial infarction in patients taking didanosine, see Effects on the Heart under Adverse Effects of Zidovudine, p.914.

Effects on the liver. Fatal fulminant hepatic failure was reported[1] in a patient receiving didanosine. A further 14 cases had been noted by the manufacturer, and elevated liver enzymes have been recorded during clinical studies.[2-5]

1. Lai KK, *et al.* Fulminant hepatic failure associated with 2′,3′-dideoxyinosine (ddI). *Ann Intern Med* 1991; **115:** 283–4.
2. Dolin R, *et al.* Zidovudine compared with didanosine in patients with advanced HIV type 1 infection and little or no experience with zidovudine. *Arch Intern Med* 1995; **155:** 961–74.
3. Jablonowski H, *et al.* A dose comparison study of didanosine in patients with very advanced HIV infection who are intolerant to or clinically deteriorate on zidovudine. *AIDS* 1995; **9:** 463–9.
4. Alpha International Coordinating Committee. The Alpha trial: European/Australian randomized double-blind trial of two doses of didanosine in zidovudine-intolerant patients with symptomatic HIV disease. *AIDS* 1996; **10:** 867–80.
5. Gatell JM, *et al.* Switching from zidovudine to didanosine in patients with symptomatic HIV infection and disease progression. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996; **12:** 249–58.

Effects on mental state. Recurrent mania associated with didanosine treatment has been reported in a patient.[1]

1. Brouillette MJ, *et al.* Didanosine-induced mania in HIV infection. *Am J Psychiatry* 1994; **151:** 1839–40.

Effects on metabolism. Hyperuricaemia has been reported to be a common adverse effect during clinical studies of didanosine.[1,2] Hypokalaemia occurred during didanosine therapy in 3 patients, 2 of whom had diarrhoea.[3] There has also been a report of hypertriglyceridaemia occurring on 2 occasions in a patient

given didanosine;[4] it was suggested that this hyperlipidaemic effect might be a possible aetiological factor in the development of pancreatitis.

1. Cooley TP, *et al.* Once-daily administration of 2′,3′-dideoxyinosine (ddI) in patients with the acquired immunodeficiency syndrome or AIDS-related complex: results of a phase I trial. *N Engl J Med* 1990; **322:** 1340–5.
2. Montaner JSG, *et al.* Didanosine compared with continued zidovudine therapy for HIV-infected patients with 200 to 500 CD4 cells/mm : a double-blind, randomized, controlled trial. *Ann Intern Med* 1995; **123:** 561–71.
3. Katlama C, *et al.* Dideoxyinosine-associated hypokalaemia. *Lancet* 1991; **337:** 183.
4. Tal A, Dall L. Didanosine-induced hypertriglyceridemia. *Am J Med* 1993; **95:** 247.

Effects on the mouth. Xerostomia (dry mouth) may be a troublesome effect in patients receiving didanosine.[1,2]

1. Dodd CL, *et al.* Xerostomia associated with didanosine. *Lancet* 1992; **340:** 790.
2. Valentine C, *et al.* Xerostomia associated with didanosine. *Lancet* 1992; **340:** 1542.

Effects on the nervous system. Peripheral neuropathy is a well recognised adverse effect of didanosine and has been the subject of a review.[1]

1. Moyle GJ, Sadler M. Peripheral neuropathy with nucleoside antiretrovirals: risk factors, incidence and management. *Drug Safety* 1998; **19:** 481–94.

Effects on the pancreas. Pancreatitis is recognised as being the most serious adverse effect of didanosine and can be fatal.[1-3] It appears to be dose-related, occurring in up to 13% of patients receiving 750 mg of didanosine daily.[2,4] Pancreatitis can resolve if didanosine is withdrawn[5] and cautious reintroduction of didanosine has been possible in some patients.[6] Raised amylase concentrations[3] and glucose intolerance have been reported in patients who subsequently developed pancreatitis.

1. Bouvet E, *et al.* Fatal case of 2′,3′-dideoxyinosine-associated pancreatitis. *Lancet* 1990; **336:** 1515.
2. Kahn JO, *et al.* A controlled trial comparing continued zidovudine with didanosine in human immunodeficiency virus infection. *N Engl J Med* 1992; **327:** 581–7.
3. Dolin R, *et al.* Zidovudine compared with didanosine in patients with advanced HIV-type 1 infection and little or no previous experience with zidovudine. *Arch Intern Med* 1995; **155:** 961–74.
4. Jablonowski H, *et al.* A dose comparison study of didanosine in patients with very advanced HIV infection who are intolerant to or clinically deteriorate on zidovudine. *AIDS* 1995; **9:** 463–9.
5. Nguyen B-Y, *et al.* Five-year follow-up of a phase I study of didanosine in patients with advanced human immunodeficiency virus infection. *J Infect Dis* 1995; **171:** 1180–9.
6. Butler KM, *et al.* Pancreatitis in human immunodeficiency virus-infected children receiving dideoxyinosine. *Pediatrics* 1993; **91:** 747–51.

Effects on the skin. Didanosine has been implicated in a case of Stevens-Johnson syndrome[1] and of cutaneous vasculitis.[2]

1. Parneix-Spake A, *et al.* Didanosine as probable cause of Stevens-Johnson syndrome. *Lancet* 1992; **340:** 857–8.
2. Herranz P, *et al.* Cutaneous vasculitis associated with didanosine. *Lancet* 1994; **344:** 680.

Precautions

Didanosine should be used with extreme caution in patients with a history of pancreatitis and those with increased triglyceride concentrations should be observed carefully for signs of pancreatitis and treatment with didanosine interrupted in all patients with signs and symptoms of possible pancreatitis, until it has been excluded. Use with other drugs likely to cause pancreatitis or peripheral neuropathy (see Interactions, below) should preferably be avoided; treatment with didanosine should be suspended if possible when use of such drugs is essential.

It may be necessary to interrupt didanosine treatment in patients who develop peripheral neuropathy; on recovery from peripheral neuropathy a reduced dose may be tolerated. Treatment should also be interrupted if uric acid concentrations are elevated.

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. Didanosine should be given with caution to patients with hepatomegaly or other risk factors for liver disease and patients with renal or hepatic impairment; dosage reduction may be necessary. Regular checks of liver function are recommended. If liver enzymes increase to 5 times the upper limit of normal during treatment then didanosine should be stopped. Treatment with didanosine may be associated with lactic acidosis and should also be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly, steatosis, or metabolic or lactic acidosis of unknown aetiology.

Children should be monitored for retinal lesions and didanosine withdrawn if they occur. Monitoring should also be considered in adults.

Interactions

Use of didanosine with other drugs known to cause pancreatitis (for example intravenous pentamidine) or with drugs that may cause peripheral neuropathy (for example metronidazole, isoniazid, and vincristine) should be avoided. If co-administration is unavoidable, patients should be monitored carefully for these adverse effects.

An increase in the area under the plasma concentration-time curve for didanosine has been reported when allopurinol or other xanthine oxidase inhibitors are given concurrently.

Plasma concentrations of didanosine may be reduced by methadone and increased by ganciclovir.

Didanosine formulations (chewable or dispersible preparation) contain an antacid and other drugs that could be affected by an increased gastric pH (for example HIV-protease inhibitors, ketoconazole, fluoroquinolone antibacterials, and dapsone) should be given at least 2 hours before didanosine. Didanosine preparations containing magnesium or aluminium antacids should not be given with tetracyclines.

Use of didanosine with tenofovir results in increased plasma concentrations of didanosine and consequently an increased risk of didanosine-related adverse effects such as peripheral neuropathy, pancreatitis, and lactic acidosis. Fatalities have been reported. There have also been reports of virological failure and emergence of resistance at an early stage of treatment when didanosine and tenofovir were given with lamivudine as part of a once daily triple nucleoside regimen. UK licensed product information for both didanosine and tenofovir does not recommend co-administration of these drugs either at standard or reduced doses of didanosine. A 250 mg daily dose of didanosine had been evaluated, but resulted in virological failure and the emergence of resistance. US product information for didanosine, however, recommends that co-administration may be undertaken with caution in patients with normal renal function. For patients weighing greater than 60 kg the dose of didanosine should be reduced to 250 mg daily, while for those weighing less than 60 kg a dose of 200 mg daily is recommended. US product information for tenofovir advises against using didanosine with tenofovir in patients under 60 kg due to a lack of data.

Ribavirin has been shown *in vitro* to increase the intracellular triphosphate levels of didanosine and to potentially increase the risk of adverse effects related to didanosine. UK product information for didanosine recommends that co-administration be undertaken with caution, while the US information does not recommend use of the two drugs together.

See also below for interactions with antivirals.

Antidiabetics. Fatal lactic acidosis has been reported[1] in a patient given *metformin* with didanosine, stavudine, and tenofovir.

1. Worth L, *et al.* A cautionary tale: fatal lactic acidosis complicating nucleoside analogue and metformin therapy. *Clin Infect Dis* 2003; **37:** 315–16.

Antivirals. Plasma concentrations of didanosine are roughly doubled when given *ganciclovir*.[1-3] *Valganciclovir*, the prodrug of ganciclovir, inhibits purine nucleoside phosphorylase and increases didanosine concentrations. Significant CD4+ T lymphocyte count decline and symptoms of didanosine toxicity, despite complete viral suppression, occurred in an HIV-positive patient given an antiretroviral regimen containing didanosine plus valganciclovir for the treatment of CMV enteritis. Complete CD4+ count recovery and resolution of symptoms occurred when didanosine was replaced with abacavir.[4]

Changes in the pharmacokinetics of didanosine and *zidovudine* have occurred when these drugs are given together, but results of studies have not been consistent, and the effects have generally been of limited clinical significance. For further details, see under Interactions in Zidovudine, p.915.

Tenofovir has been reported to significantly increase plasma concentrations of didanosine,[5] and may increase the risk of pancreatitis associated with didanosine.[6,7] There has also been a report of acute renal failure and fatal lactic acidosis when tenofovir was added to a regimen containing didanosine.[8]

Use of didanosine with *delavirdine* resulted in reductions in the area under the concentration-time curve for both drugs in a single-dose study.[9] Licensed product information for delavirdine recommends that these two drugs should be given at least 1 hour apart.

Absorption of some *HIV-protease inhibitors* may be reduced by the buffers in some didanosine formulations and doses should be at least 2 hours apart (see p.883).

1. Griffy KG. Pharmacokinetics of oral ganciclovir capsules in HIV-infected persons. *AIDS* 1996; **10** (suppl 4): S3–S6.
2. Jung D, *et al.* Effect of high-dose oral ganciclovir on didanosine disposition in human immunodeficiency virus (HIV)-positive patients. *J Clin Pharmacol* 1998; **38:** 1057–62.
3. Cimoch PJ, *et al.* Pharmacokinetics of oral ganciclovir alone and in combination with zidovudine, didanosine, and probenecid in HIV-infected subjects. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; **17:** 227–34.
4. Tseng AL, Salit IE. CD4+ cell count decline despite HIV suppression: a probable didanosine-valganciclovir interaction. *Ann Pharmacother* 2007; **41:** 512–17.
5. Pecora Fulco P, Kirian MA. Effect of tenofovir on didanosine absorption in patients with HIV. *Ann Pharmacother* 2003; **37:** 1325–8.
6. Blanchard JN, *et al.* Pancreatitis with didanosine and tenofovir disoproxil fumarate. *Clin Infect Dis* 2003; **37:** e57–e62. Correction. *ibid.*: 995. [title of paper corrected]
7. Kirian MA, *et al.* Acute onset of pancreatitis with concomitant use of tenofovir and didanosine. *Ann Pharmacother* 2004; **38:** 1660–3.
8. Murphy MD, *et al.* Fatal lactic acidosis and acute renal failure after addition of tenofovir to an antiretroviral regimen containing didanosine. *Clin Infect Dis* 2003; **36:** 1082–5.
9. Morse GD, *et al.* Single-dose pharmacokinetics of delavirdine mesylate and didanosine in patients with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1997; **41:** 169–74.

Antiviral Action

Didanosine is converted intracellularly to its active form dideoxyadenosine triphosphate. This triphosphate halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA.

Didanosine-resistant strains of HIV emerge during didanosine therapy. Cross-resistance to other nucleoside reverse transcriptase inhibitors has been recognised.

Resistance. Evidence for the development of didanosine-resistant HIV was reported in 36 of 64 patients with advanced HIV infection within 24 weeks of switching from zidovudine to didanosine monotherapy.[1] Patients with the didanosine resistance mutation for HIV reverse transcriptase showed a greater decline in CD4+ T cell count and increase in viral burden than those without.

Multiple-drug resistant mutations have been found in patients taking long-term combination antiretroviral therapy containing didanosine.[2]

1. Kozal MJ, *et al.* Didanosine resistance in HIV-infected patients switched from zidovudine to didanosine monotherapy. *Ann Intern Med* 1994; **121:** 263–8.
2. Kavlick MF, *et al.* Emergence of multi-dideoxynucleoside-resistant human immunodeficiency virus type 1 variants, viral sequence variation, and disease progression in patients receiving antiretroviral chemotherapy. *J Infect Dis* 1998; **98:** 1506–13.

Pharmacokinetics

Didanosine is rapidly hydrolysed in the acid medium of the stomach and is therefore given orally with pH buffers or antacids. Bioavailability is reported to range from 20 to 40% depending on the formulation used; the bioavailability is substantially reduced if taken with or after food. Maximum plasma concentrations are achieved about 1 hour after oral dosage. Binding to plasma proteins is reported to be less than 5%. Didanosine has been reported not to cross the blood brain barrier.

Didanosine is metabolised intracellularly to the active antiviral metabolite dideoxyadenosine triphosphate. The plasma elimination half-life is reported to be about 1.5 hours. Renal clearance is by glomerular filtration and active tubular secretion; about 20% of an oral dose is recovered in the urine. Didanosine is partially cleared by haemodialysis but not by peritoneal dialysis.

◊ References.

1. Balis FM, *et al.* Clinical pharmacology of 2′,3′-dideoxyinosine in human immunodeficiency virus-infected children. *J Infect Dis* 1992; **165:** 99–104.
2. Morse GD, *et al.* Comparative pharmacokinetics of antiviral nucleoside analogues. *Clin Pharmacokinet* 1993; **24:** 101–23.
3. Mueller BU, *et al.* Clinical and pharmacokinetic evaluation of long-term therapy with didanosine in children with HIV infection. *Pediatrics* 1994; **94:** 724–31.

4. Knupp CA, *et al.* Disposition of didanosine in HIV-seropositive patients with normal renal function or chronic renal failure: influence of hemodialysis and continuous ambulatory peritoneal dialysis. *Clin Pharmacol Ther* 1996; **60:** 535–42.
5. Wintergerst U, *et al.* Lack of absorption of didanosine after rectal administration in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 1999; **43:** 699–701.
6. Abreu T, *et al.* Bioavailability of once- and twice-daily regimens of didanosine in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother* 2000; **44:** 1375–6.

Pregnancy. Fetal blood concentrations of 14 and 19% of the maternal serum-didanosine concentrations have been reported.[1] There is evidence of extensive metabolism in the placenta.[2]

1. Pons JC, *et al.* Fetoplacental passage of 2′,3′-dideoxyinosine. *Lancet* 1991; **337:** 732.
2. Dancis J, *et al.* Transfer and metabolism of dideoxyinosine by the perfused human placenta. *J Acquir Immune Defic Syndr* 1993; **6:** 2–6.

Uses and Administration

Didanosine is a nucleoside reverse transcriptase inhibitor structurally related to inosine with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when didanosine is used alone, and it is therefore used with other antiretrovirals.

Didanosine is given orally, usually as buffered chewable/dispersible tablets or enteric-coated capsules. Doses should be taken at least 30 minutes before, or 2 hours after, a meal. The total daily dose may be given as either a single dose or as two divided doses, the choice being dependent upon both the formulation and the strength used. For adults weighing more than 60 kg the recommended dose is 400 mg daily and for those under 60 kg, 250 mg daily is given.

For details of doses in children, see below.

Doses of didanosine may need to be amended when given with some other antiretrovirals. For further details see under Interactions, above.

Dosage reduction may be necessary in patients with renal (see below) or hepatic impairment, although no specific dose reductions are recommended in patients with hepatic impairment and close monitoring is required.

◊ Reviews.

1. Shelton MJ, *et al.* Didanosine. *Ann Pharmacother* 1992; **26:** 660–70.
2. Lipsky JJ. Zalcitabine and didanosine. *Lancet* 1993; **341:** 30–2.
3. Perry CM, Noble S. Didanosine: an updated review of its use in HIV infection. *Drugs* 1999; **58:** 1099–1135.
4. Moreno S, *et al.* Didanosine enteric-coated capsule: current role in patients with HIV-1 infection. *Drugs* 2007; **67:** 1441–62.

Administration in children. For the treatment of HIV infection in children, didanosine is given daily with other antiretroviral drugs in doses based on body-surface. Doses are taken on an empty stomach. In the USA an oral solution is available for paediatric use:

- in children aged between 2 weeks and 8 months the recommended dose is 100 mg/m^2 twice daily
- in children over 8 months of age the recommended dose is 120 mg/m^2 twice daily

In the UK chewable or dispersible tablets or enteric-coated capsules are available for use:

- the chewable or dispersible tablets may be given orally to children older than 3 months of age, as either a single dose or as two divided doses, in a dose of 240 mg/m^2 daily *or* 180 mg/m^2 daily if given with zidovudine
- enteric-coated capsules may be given orally to children older than 6 years of age in a dose of 240 mg/m^2 daily *or* 180 mg/m^2 daily if given with zidovudine

Administration in renal impairment. Dosage of didanosine should be reduced in patients with renal impairment. The following doses are recommended based on the patient's creatinine clearance (CC):

Adults greater than 60 kg:

- CC more than 60 mL/minute: usual adult doses
- CC 30 to 59 mL/minute: 200 mg daily as a single dose or in two equally divided doses
- CC 10 to 29 mL/minute: 150 mg once daily
- CC less than 10 mL/minute: 100 mg once daily

Adults less than 60 kg:

- CC more than 60 mL/minute: usual adult doses
- CC 30 to 59 mL/minute: 150 mg daily as a single dose or in two equally divided doses
- CC 10 to 29 mL/minute: 100 mg once daily
- CC less than 10 mL/minute: 75 mg once daily

Preparations

USP 31: Didanosine for Oral Solution; Didanosine Tablets for Oral Suspension.

Proprietary Preparations (details are given in Part 3)

Arg.: Aso DDI†; Bandotan†; Dibistic†; Megavir†; Ronvir†; Videx; ***Austral.:*** Videx; ***Austria:*** Videx; ***Belg.:*** Videx; ***Braz.:*** Didanox†; Videx; ***Canad.:*** Videx; ***Chile:*** Videx; ***Cz.:*** Videx; ***Denm.:*** Videx; ***Fin.:*** Videx; ***Fr.:*** Videx; ***Ger.:*** Videx; ***Gr.:*** Videx; ***Hong Kong:*** Videx; ***Hung.:*** Videx; ***India:*** Dinex; ***Indon.:*** Videx; ***Irl.:*** Videx; ***Israel:*** Videx†; ***Ital.:*** Videx; ***Malaysia:*** Videx; ***Mex.:*** Apodasi†; Didasten; Videx; ***Neth.:*** Videx; ***Norw.:*** Videx; ***NZ:*** Videx; ***Pol.:*** Videx; ***Port.:*** Videx; ***Rus.:*** Videx (Видекс); ***S.Afr.:*** Videx; ***Singapore:*** Videx; ***Spain:*** Videx; ***Swed.:*** Videx; ***Switz.:*** Videx; ***Thai.:*** Videx; ***Turk.:*** Videx; ***UK:*** Videx; ***USA:*** Videx; ***Venez.:*** Videx.

Multi-ingredient: ***India:*** Odivir Kit.

Docosanol *(USAN)*

Behenyl Alcohol; *n*-Docosanol; Docosyl Alcohol; lK-2. 1-Docosanol.

Докозанол

$C_{22}H_{46}O$ = 326.6.

CAS — 661-19-8.

ATC — D06BB11.

ATC Vet — QD06BB11.

Profile

Docosanol is an antiviral used topically five times daily as a 10% cream in the treatment of recurrent herpes labialis (p.854). Docosanol acts by inhibiting fusion between the cell plasma membrane and the herpes simplex virus, thereby preventing viral entry into cells and subsequent viral replication. It has been investigated for genital herpes.

◊ References.

1. Habbema L, *et al.* n-Docosanol 10% cream in the treatment of recurrent herpes labialis: a randomised, double-blind, placebo-controlled study. *Acta Derm Venereol* 1996; **76:** 479–81.
2. Sacks SL, *et al.* Clinical efficacy of topical docosanol 10% cream for herpes simplex labialis: a multicenter, randomized, placebo-controlled trial. *J Am Acad Dermatol* 2001; **45:** 222–30.
3. Leung DT, Sacks SL. Docosanol: a topical antiviral for herpes labialis. *Expert Opin Pharmacother* 2004; **5:** 2567–71.

Preparations

Proprietary Preparations (details are given in Part 3)

Canad.: Abreva; ***Cz.:*** Erazaban; ***Gr.:*** Healip; ***Swed.:*** Healip; ***USA:*** Abreva.

Edoxudine *(USAN, rINN)*

Edoxudina; Édoxudine; Edoxudinum; EDU; Ethyl Deoxyuridine; EUDR; ORF-15817; RWJ-15817. 2′-Deoxy-5-ethyluridine.

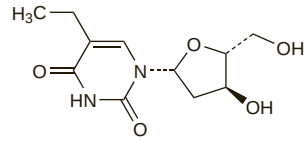
Эдоксудин

$C_{11}H_{16}N_2O_5$ = 256.3.

CAS — 15176-29-1.

ATC — D06BB09.

ATC Vet — QD06BB09.



Profile

Edoxudine is an antiviral that has been used topically in the treatment of mucocutaneous herpes simplex infections (p.854); it has also been used as an ophthalmic preparation.

Preparations

Proprietary Preparations (details are given in Part 3)

Switz.: Edurid†.

Efavirenz *(BAN, rINN)*

5B706; DMP-266; Efavirentsi; Éfavirenz; Efavirenzum; L-743; L-743726. (*S*)-6-Chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one.

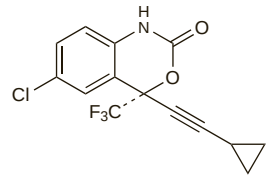
Эфавиренз

$C_{14}H_9ClF_3NO_2$ = 315.7.

CAS — 154598-52-4.

ATC — J05AG03.

ATC Vet — QJ05AG03.



Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing efavirenz are skin rashes and psychiatric or CNS disturbances. Mild to moderate rashes (usually maculopapular eruptions) generally appear within the first 2 weeks of starting therapy and may resolve within a month of continued treatment; of severe forms including erythema multiforme and Stevens-Johnson syndrome have been reported occasionally. CNS symptoms include agitation, amnesia, confusion, dizziness, euphoria, headache, insomnia or somnolence, impaired concentration, abnormal thinking or dreaming, convulsions, depersonalisation, and hallucinations. Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2 to 4 weeks; they may occur more frequently when efavirenz is taken with meals, possibly due to increased efavirenz plasma concentrations. Serious psychiatric adverse effects include severe depression, suicidal ideation and attempts, aggressive behaviour, and psychotic reactions including paranoia and mania. Other adverse effects include nausea and vomiting, diarrhoea, fatigue, and pancreatitis. Raised liver enzyme values and raised serum-cholesterol and -triglyceride concentrations have been reported. Hepatic failure and photoallergic dermatitis have 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 efavirenz, 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 efavirenz. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported.

◊ References.

1. Clifford DB, *et al.* Impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals. *Ann Intern Med* 2005; **143:** 714–21.

Effects on the mouth. Burning mouth syndrome was diagnosed in a patient 2 weeks after adding efavirenz to her longstanding combination antiretroviral treatment regimen.[1] Efavirenz was stopped and the syndrome resolved within 1 week.

1. Borrás-Blasco J, *et al.* Burning mouth syndrome due to efavirenz therapy. *Ann Pharmacother* 2006; **40:** 1471–2.

Precautions

Efavirenz is contra-indicated in patients with severe hepatic impairment (Child-Pugh class C), and should be used with caution, and liver enzymes 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 should be exercised in patients