

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 H₂-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, methylethergometrine), 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 drugs¹ 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.

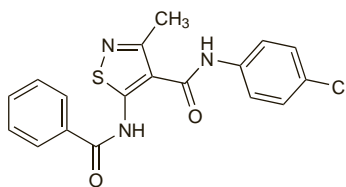
Denotivir (pINN)

Dénovir; Denotivirum. 5-Benzamido-4'-chloro-3-methyl-4-isothiazolecarboxanilide.

ДЕНОТИВИР

C₁₈H₁₄ClN₃O₂S = 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)

BMV-40900; ddi; ddln; Didanocin; Didanosini; Didanosin; Didanosina; Didanosinum; Didanozin; Didanozinas; Dideoxyinosine; NSC-612049. 2',3'-Dideoxyinosine.

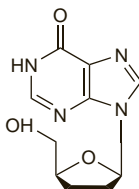
ДИДАНОЗИН

C₁₀H₁₂N₄O₃ = 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 pan-

creatitis. 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/m² 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 reported¹ 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