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.

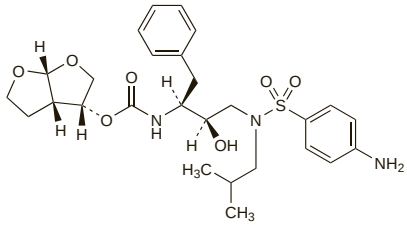
Дарунавир

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

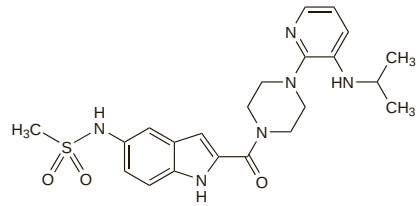
Делавирдина Мезилат

$C_{22}H_{28}N_6O_3S,CH_4O_3S$ = 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-

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

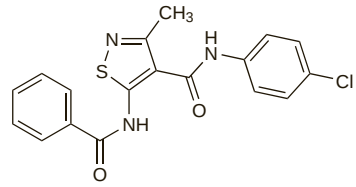
Proprietary Preparations (details are given in Part 3)
Austral.: Rescriptor; ***Canad.:*** Rescriptor; ***Mex.:*** Rescriptor†; ***USA:*** Rescriptor.

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

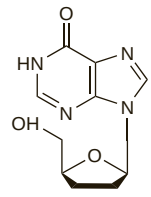
Proprietary Preparations (details are given in Part 3)
Pol.: Polvir; Vratizolin.

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