

Didanosine

Brand Name: Videx, Videx EC

Drug Description

Didanosine is a synthetic analogue of deoxyadenosine, a naturally occurring purine nucleoside. Didanosine differs from deoxyadenosine in that the 3'-hydroxyl group on the ribose moiety is replaced with hydrogen. [1]

HIV/AIDS-Related Uses

Didanosine was approved by the FDA on October 9, 1991, and enteric-coated didanosine was approved by the FDA on October 31, 2000.[2] Didanosine is used in conjunction with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients.[3]

Didanosine is used with stavudine for postexposure prophylaxis of HIV infection in healthcare workers and other individuals exposed occupationally via percutaneous injury or mucous membrane or nonintact skin contact with tissues or body fluids associated with a risk of HIV transmission.[4]

Pharmacology

Didanosine is converted by cellular enzymes to the active metabolite dideoxyadenosine 5'-triphosphate (ddA-TP), which inhibits HIV-1 reverse transcriptase by competing with the natural substrate, deoxyadenosine 5'-triphosphate, for incorporation into viral DNA. Once incorporated, ddA-TP causes termination of viral DNA synthesis.[5] [6]

Didanosine is rapidly absorbed, with peak plasma concentrations (C_{max}) observed from 0.25 to 1.50 hours following oral dosing with a buffered formulation and 2 hours following oral dosing with the enteric-coated formulation.[7] Extent of absorption depends on several factors, including dosage form, gastric pH, and presence of food in the gastrointestinal (GI) tract.[8]

Didanosine's C_{max} and area under the plasma-concentration curve (AUC) were decreased by approximately 55% when didanosine buffered tablets were administered up to 2 hours after a meal. Administration of didanosine tablets up to 30

minutes before a meal did not result in any significant changes in bioavailability.[9] The C_{max} and AUC for the enteric-coated formulation were reduced by approximately 46% and 19%, respectively, in the presence of food.[10]

Because gastric secretions may inactivate didanosine following oral administration, didanosine chewable/dispersible tablets and powder for oral solution either contain buffering agents or must be admixed with antacids prior to administration.[11] The delayed-release capsules contain enteric-coated pellets, which protect didanosine from degradation by stomach acid. The enteric-coated pellets dissolve when the pellets reach the small intestine, the site of drug absorption.[12]

Didanosine is distributed into cerebrospinal fluid (CSF); CSF concentrations average 21% of concurrent plasma concentrations in samples obtained 1 hour after a single IV dose. In a study of HIV infected pediatric patients who received oral or intravenous didanosine, CSF concentrations averaged 46% (range: 12% to 85%) of concurrent plasma concentrations.[13] Binding of didanosine to plasma proteins in vitro is less than 5%.[14]

Didanosine is in FDA Pregnancy Category B. No adequate or well-controlled studies of didanosine have been done in pregnant women. In animal studies, didanosine and/or its metabolites were transferred to the fetus through the placenta. Animal studies with didanosine have not shown evidence of impaired fertility or harm to the fetus. Nevertheless, the drug should be used during pregnancy only if clearly needed. To monitor maternal-fetal outcomes of pregnant women exposed to didanosine and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians may register patients by calling 1-800-258-4263. [15] It is not known whether didanosine or its metabolites are distributed into human milk; however, the drug and/or its metabolites are distributed into milk in laboratory animals.[16]

The metabolic fate of didanosine has not been fully evaluated in humans. Because didanosine is an

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Pharmacology (cont.)

analogue of a naturally occurring purine nucleoside, metabolism of the drug is presumed to occur via the same pathways as endogenous purines. The in vivo intracellular half-life of the active metabolite, ddA-TP, has not been determined; the in vitro intracellular half-life of ddA-TP is 8 to 24 hours. In HIV infected adults, the plasma half-life of didanosine averages 0.97 to 1.6 hours. In HIV infected pediatric patients, the plasma half-life averages 0.8 hours.[17]

Didanosine is eliminated in urine by glomerular filtration and active tubular secretion. Following oral dosing in adults, the renal clearance of didanosine is approximately 50% of the total body clearance and averages 400 ml/min. Renal clearance has been reported to average 5.5 ml/min/kg in adult patients and 240 ml/min/m² in pediatric patients. In HIV infected adults, approximately 20% of the dose is eliminated in the urine; in pediatric patients approximately 18% of the dose is eliminated in the urine.[18]

The half-life of didanosine increases as creatinine clearance decreases. It is recommended that the didanosine dose be modified in patients with renal impairment and reduced creatinine clearance and in patients receiving maintenance hemodialysis.[19] [20] The effects of impaired hepatic function on the pharmacokinetics of didanosine have not been adequately studied.[21]

HIV-1 isolates with reduced sensitivity to didanosine have been selected in vitro and were also obtained from patients treated with didanosine. Phenotypic analysis of HIV-1 isolates from 60 patients receiving from 6 to 24 months of didanosine monotherapy, some with prior exposure to zidovudine, showed that isolates from 10 of 60 patients exhibited an average of a 10-fold decrease in susceptibility to didanosine in vitro compared to baseline isolates.

HIV-1 isolates from 2 of 39 patients receiving combination therapy with zidovudine and didanosine for up to 2 years exhibited cross-resistance to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine in vitro. The clinical relevance of these observations has not

been established.[22] [23]

Adverse Events/Toxicity

Pancreatitis, which has been fatal in some cases, is one of the most serious adverse effects reported in patients receiving didanosine.[24] The frequency of pancreatitis is dose-related, with an incidence in adult patients between 1% and 7% and in pediatric patients between 3% and 13%. Pancreatitis has occurred during didanosine therapy in both treatment-experienced and treatment-naïve patients, regardless of the degree of immunosuppression. Didanosine treatment should be suspended in patients with suspected pancreatitis and discontinued in patients with confirmed pancreatitis.[25]

The use of didanosine and other nucleoside analogues, either alone or in combination with other antiretrovirals, has been associated with lactic acidosis and severe hepatomegaly with steatosis, including some fatal cases. Risk factors include female gender, obesity, and prolonged exposure to antiretroviral nucleoside analogues. Fatal lactic acidosis has been reported in pregnant women who received an antiretroviral regimen that included didanosine and stavudine. Cases have occurred in patients with and without known risk factors for liver disease. Didanosine use should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity, which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations.[26]

Peripheral neuropathy, manifested by numbness, tingling, or pain in the hands or feet, has been reported in patients taking didanosine. In recent studies, peripheral neuropathy was reported in 21% to 26% of patients taking didanosine in conjunction with stavudine and either nelfinavir or indinavir.[27]

Common, less serious adverse effects include central nervous system effects (anxiety, headache, insomnia, irritability, and restlessness); dry mouth; gastrointestinal disturbances (diarrhea, dyspepsia, flatulence, nausea, vomiting); and skin rash.[28] [29]

Other, less frequently reported, effects involve the

Adverse Events/Toxicity (cont.)

following organ systems: body as a whole (alopecia, anaphylactoid reaction, asthenia, chills/fever, pain, redistribution/accumulation of body fat)[30] ; cardiovascular (cardiomyopathy); exocrine (sialoadenitis, parotid gland enlargement, dry mouth); hematologic (anemia, leukopenia, thrombocytopenia); metabolic (hyperglycemia, hypoglycemia, diabetes mellitus); musculoskeletal (myalgia, rhabdomyolysis with acute renal failure, arthralgia, myopathy); and ocular (retinal changes, optic neuritis, diplopia, dry eyes, optic atrophy, and blindness).[31]

Drug and Food Interactions

Presence of food in the GI tract decreases the rate and extent of absorption of oral didanosine.[32]

Concomitant use of didanosine and drugs associated with pancreatic toxicity, such as alcohol, asparaginase, azathioprine, estrogens, furosemide, methyl dopa, nitrofurantoin, pentamidine (IV), sulfonamides, sulindac, tetracyclines, thiazide diuretics, and valproic acid, may increase the risk of pancreatitis. Didanosine should be used with extreme caution and only when other alternatives are not available in patients receiving these drugs.[33] The manufacturer suggests that didanosine be discontinued in patients who require life-sustaining treatment with other drugs known to cause pancreatitis. Patients receiving didanosine in combination with stavudine, with or without hydroxyurea, may be at an increased risk for potentially fatal pancreatitis.[34]

Didanosine should be avoided or used with caution in patients receiving other drugs that have been associated with peripheral neuropathy, such as chloramphenicol, cisplatin, dapsone, ethambutol, ethionamide, hydralazine, isoniazid, lithium, metronidazole, nitrofurantoin, nitrous oxide, phenytoin, stavudine, vincristine, and zalcitabine.[35]

When buffered preparations of didanosine are administered with medications that require an acidic environment, didanosine may cause decreased absorption of the coadministered drug. Drugs that depend on gastric acidity for optimal

absorption, including dapsone, itraconazole, and ketoconazole, should be administered at least 2 hours before or 2 hours after didanosine is given.[36] Didanosine delayed-release capsules do not affect the pharmacokinetics of ketoconazole.[37]

Coadministration of tenofovir disoproxil fumarate (TDF) with didanosine causes increased absorption of didanosine. Increased exposure may cause or worsen didanosine-related toxicities, including pancreatitis, hyperlactatemia/lactic acidosis, and peripheral neuropathy. Coadministration of TDF with didanosine should be undertaken with caution, and patients should be monitored closely for didanosine-related toxicities.[38]

In vitro studies demonstrate that concurrent administration of didanosine and oral ganciclovir resulted in a 111% increase in the steady-state AUC of didanosine and may result in increased didanosine-related toxicities. Because valganciclovir is rapidly and completely converted to ganciclovir, drug interactions associated with ganciclovir are expected to occur with valganciclovir as well. Patients receiving concomitant therapy with didanosine and ganciclovir or valganciclovir should be monitored for didanosine toxicity.[39]

Didanosine and some protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, and saquinavir) have additive or synergistic activity against HIV-1, probably due to the different stages of virus replication at which these drugs are active. However, due to the buffering agents in some didanosine dosage forms and the requirement that most protease inhibitors be administered with food, dosing of these drugs should be separated.[40]

The oral absorption and plasma concentrations of quinolone antibiotics or tetracyclines may be decreased in the presence of antacids such as those present in the buffering agents of certain oral didanosine dosage forms. Dosages of didanosine and quinolones should be separated by at least 2 hours.[41]

Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased when didanosine is coadministered with ribavirin.

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Drug and Food Interactions (cont.)

Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and hyperlactatemia/lactic acidosis have been reported in patients taking both didanosine and ribavirin. Coadministration of ribavirin with didanosine is not recommended.[42]

Concomitant use of allopurinol and didanosine is not recommended. Average AUC of didanosine was increased twofold when administered concomitantly with allopurinol in healthy adults. Concomitant use of didanosine and methadone appears to decrease bioavailability of didanosine.[43]

Based on data from an open-label randomized study and retrospective database analyses, clinicians are advised to use caution when administering enteric-coated didanosine, TDF, and either efavirenz or nevirapine in the treatment of treatment naive HIV infected patients with high baseline viral loads.[44]

Contraindications

Didanosine is contraindicated in patients with previously demonstrated, clinically significant hypersensitivity to any component of the formulation.[45] [46] Patients with phenylketonuria should be made aware that didanosine chewable/dispersible buffered tablets contain aspartame (NutraSweet).[47]

Clinical Trials

For information on clinical trials that involve Didanosine, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Didanosine AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[48]

Dosage Form: Chewable/dispersible buffered tablets containing 25, 50, 100, 150, or 200 mg of didanosine; buffered powder for oral solution in single-dose packets containing 100, 167, or 250 mg of didanosine; pediatric powder for oral solution in 4- or 8-ounce bottles containing 2 g or 4 g of

didanosine, respectively; or delayed-release capsules of enteric-coated beadlets containing 125, 200, 250, or 400 mg of didanosine.

The recommended doses of didanosine are dependent on drug form and patient weight. For adults weighing 60 kg (132 lbs) or more, the recommended doses are 200 mg twice daily (tablets), 250 mg twice daily (buffered powder), or 400 mg once daily (enteric-coated capsules). For adults weighing less than 60 kg (132 lbs), the recommended doses are 125 mg twice daily (tablets), 167 mg twice daily (buffered powder), or 250 mg once daily (enteric-coated capsules). The recommended dose of didanosine in pediatric patients age 2 weeks to 8 months is 100 mg/m² twice daily, and the recommended dose for pediatric patients older than 8 months is 120 mg/m² twice daily.

In patients with impaired renal function, the doses and dosing intervals of didanosine should be adjusted to compensate for the slower rate of elimination. Recommendations for didanosine dosing in renal impairment are provided in the Videx and Videx EC prescribing information.[49] [50]

Storage: Store didanosine chewable/dispersible tablets and powder for oral solution between 15 and 30 C (59 and 86 F).[51] Delayed-release capsules should be stored at 25 C (77 F), with excursions between 15 and 30 C (59 and 86 F) permitted.[52]

Chemistry

CAS Name: Inosine, 2',3'-dideoxy-[53]

CAS Number: 69655-05-6[54]

Molecular formula: C₁₀H₁₂N₄O₃[55]

C50.84%, H5.12%, N23.72%, O20.32% [56]

Molecular weight: 236.23[57]

Melting point: 160-163 C[58]

Physical Description: White, nonhygroscopic crystalline powder.[59]

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Chemistry (cont.)

Stability: Didanosine is stable at neutral or slightly alkaline pH, but is unstable at acid pH. Solutions made from didanosine chewable/dispersible buffered tablets that have been dispersed in water or further dispersed in 30 ml of apple juice are stable for 1 hour at room temperature. Solutions made from didanosine buffered powder for oral solution are stable for 4 hours at room temperature when reconstituted with water. After reconstitution with the appropriate admixture of water and liquid antacid, the resulting suspension of didanosine pediatric powder for oral solution may be stored for up to 30 days in a refrigerator at 2 to 8 C (36 to 46 F). Discard any unused portion after 30 days.[60]

Solubility: 27.3 mg/ml in water at 25 C.[61]

Other Names

BMY 40900[62]

CCRIS 805[63]

ddI[64]

Dideoxyinosine[65]

2',3'-Dideoxyinosine[66]

BRN 3619529[67]

HSDB 6548[68]

NSC 612049[69]

Further Reading

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Manufacturer Information

Didanosine
Bristol - Myers Squibb Co
PO Box 4500
Princeton, NJ 08543-4500
(800) 321-1335

Videx
Bristol - Myers Squibb Co
PO Box 4500
Princeton, NJ 08543-4500
(800) 321-1335

Videx EC
Bristol - Myers Squibb Co
PO Box 4500
Princeton, NJ 08543-4500
(800) 321-1335

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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