Didanosine (Videx®, ddI)

Class:
Didanosine is a nucleoside analogue.

Antiviral Activity:
Didanosine has been evaluated and shown to be active against HIV-1.

Mechanism of Action:
Nucleoside Reverse Transcriptase Inhibitor (NRTI).
Didanosine in converted to dideoxyadenosine-triphosphate (ddATP), which competes with endogenous nucleotides for incorporation into the viral DNA and once incorporated causes chain termination due to the lack of a 3' OH group.

Mechanism of Resistance:
Resistance to NRTIs occurs through two mechanisms; decreased incorporation of NRTIs into the viral DNA and increased excision of NRTIs from the viral DNA.

Pharmacodynamics:
In vitro IC_{50} (50% inhibitory concentration) range was 2.5 to 10 uM (1 uM = 0.24 mcg/mL) in lymphoblastic cells and 0.01 uM to 0.1 uM in monocytic cells.

Pharmacokinetics:
Didanosine is susceptible to acid hydrolysis and is degraded rapidly at low gastric pH (pH < 3). The plasma half-life of didanosine is 0.8 to 1.9 hours after a single dose and 1.1 to 2.7 hours after multiple dosing. *In vitro* plasma protein binding has been estimated at <5%. Renal clearance is responsible for 30-50% of the total body clearance of didanosine. The remainder is eliminated through metabolism and biliary excretion. Active tubular excretion seems to attribute to the renal clearance.

Adverse Effects:
Didanosine therapy is associated with peripheral neuropathy, pancreatitis, hyperamylasemia, hyperuricemia and gastrointestinal complaints. Hepatic toxicity, rare cases of electrolyte imbalances and cardiac arrhythmias have also been seen. Dry mouth, altered taste, decreased palatability and nausea are more common with the buffered formulation.

Dosage:
chewable, dispersible buffered tablet 25, 50, 100, 150, 200 mg
packets of buffered powder for oral solution 100, 167, 250 mg
pediatric powder for oral solution 10 mg/mL
Enteric coated capsule 125, 200, 250, 400 mg (30 capsule bottles)

Adults:
Videx®

Chewable, dispersible buffered tablet:
= 60 kg: 200 mg twice daily or 400 mg once daily
< 60 kg: 125 mg twice daily or 250 mg once daily

Buffered powder for oral solution:
= 60 kg: 250 mg twice daily
< 60 kg: 167 mg twice daily

Videx® EC: = 60 kg 400 mg once daily
< 60 kg 250 mg once daily

Pediatrics:

Videx®

10 mg/mL pediatric powder for oral solution:

Neonatal/Infant aged < 90 days: 50 mg/m^2 every 12 hours

Pediatric: 120 mg/m^2 every 12 hours (Pediatric dosage range: 90 – 150 mg/m^2 every 12 hours)

Videx® EC Not studied in pediatric patients.

All formulations are to be dosed on an empty stomach, at least 30 minutes before or two hours after eating.

There is insufficient data to make dose recommendations in patients with hepatic failure.

Disease state based dosing:

Impaired Renal Function

CrCl = 60 ml/min

= 60 kg: Buffered Tablet 200mg twice daily; Buffered Powder 250mg twice daily; Enteric Coated Capsule 400mg once daily

< 60 kg: Buffered Tablet 125mg twice daily; Buffered Powder 167mg twice daily; Enteric Coated Capsule 250mg once daily

CrCl 30-59 ml/min

= 60 kg: Buffered Tablet 200mg once daily OR 100mg twice daily; Buffered Powder 100mg twice daily; Enteric Coated Capsule 200mg once daily

< 60 kg: Buffered Tablet 110mg once daily OR 75mg twice daily; Buffered Powder 100mg twice daily; Enteric Coated Capsule 125mg once daily

CrCl 10-29 ml/min

= 60 kg: Buffered Tablet 150mg once daily; Buffered Powder 167mg once daily; Enteric Coated Capsule 125mg once daily

< 60 kg: Buffered Tablet 100mg once daily; Buffered Powder 100mg once daily; Enteric Coated Capsule 125mg once daily

CrCl < 10 ml/min

= 60 kg: Buffered Tablet 100mg once daily; Buffered Powder 100mg once daily; Enteric Coated Capsule 125mg once daily

< 60 kg: Buffered Tablet 75mg once daily; Buffered Powder 100mg once daily; Enteric Coated Capsule not used

Contraindications/Warnings/Precautions:

Fatal and nonfatal pancreatitis has occurred in patients taking didanosine. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of NRTIs.

Drug Interactions:

The buffered formulation of didanosine should be separated from drugs that are optimally absorbed in the presence of a normal gastric pH (delavirdine, indinavir, ketoconazole). Oral ganciclovir may increase the didanosine concentrations by as much as 70%. Tenofovir increases the AUC of didanosine by up to 60% and ribavirin increases exposure to didanosine.

Pregnancy: Category B: No evidence of risk in humans but studies inadequate.

Monitoring Requirements:

CBC, baseline LFTs, serum amylase, baseline serum creatinine/BUN, serum potassium, serum uric acid, serum magnesium (in patients with renal impairment) and periodic retinal examinations.

Brand names/Manufacturer:

Videx®, Videx® EC - Bristol-Myers Squibb Company

Barr Laboratories (Generic didanosine delayed release capsules)