**Selected Properties of Didanosine**

***buffered tablets discontinued in Canada as of February 2006***

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| **Other names** | Videx®, Videx EC®, ddI |
| **Manufacturer** | BristolMyersSquibb |
| **Pharmacology/Mechanism of Action** | • adenine analogue, intracellular triphosphorylation to active form with preferential activity in resting cells<br>• causes viral DNA chain termination via absence of 3'-hydroxyl group to inhibit HIV reverse transcription<br>• competes with natural nucleoside substrate for binding to active site of reverse transcriptase |
| **Activity** | In vitro IC50 ranged from 2.5-10 µM (1 µM = 0.24 µg/mL) in lymphoblastic cell lines and 0.01-0.1 µM in monocyte/macrophage cell cultures. |
| **Resistance - genotypic** | Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations):<br>• K65R, L74V<br>• *Presence of 3 of the following TAMS associated with resistance to didanosine: M41L, D67N, L210W, T215Y/F, K219Q/E (K70R and M184 not associated with decreased virologic response to didanosine)*<br>• *69 Insertion Complex is associated with resistance to all approved NRTIs when present with ≥1 TAM at codons 41, 210 or 215.*<br>• *Q151M complex (with A62V, V75I, F77L, F116Y) is associated with resistance to all approved NRTIs except for tenofovir.* |
| **Resistance - phenotypic** | Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/):<br>K65R: 1.8-fold ↑ (intermediate resistance)<br>L74V: 1.6-fold ↑ (intermediate resistance)<br>L74V + M184V: 2.5-fold ↑ (intermediate resistance)<br>M184V + TAMS: ↓ didanosine susceptibility |
| **Cross-Resistance** | Cross-resistance to other nucleoside analogues possible. |
| **Oral Bioavailability** | 42%; susceptible to acid hydrolysis; food reduces absorption of buffered tablet by 50%<br>• high gastric pH rapidly achieved after oral dosing with buffered ddI tablets, but duration of elevated gastric pH was approx. 25 minutes (14-60)<br>Absorption of didanosine EC occurs mainly in the small intestine. |

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| **Effect of Food** | Take on empty stomach.<br>Buffered tablets require basic media for absorption (contains Al/Mg/Ca buffers).<br><br>Delayed release capsules have ↓ Cmax 46% and ↓ AUC 19% when taken with food compared to the fasting state. VIDEX EC should be taken on an empty stomach.<br><br>In a randomized, open-label label study of 28 days ddI monotherapy in HIV-infected, treatment-naïve subjects (n=21), mean ddI trough plasma levels at day 28 were 0.0234 mg/L for patients taking ddI on an empty stomach and 0.0227 mg/L for those taking it after a fat-rich breakfast, showing no statistically significant difference (P=0.96). There was no difference in the rate of decrease of HIV-1 RNA between the two groups (Hernandez-Novoa et al. 2008). |
| **Protein Binding** | <5% |
| **Vd** | 1.08L/kg |
| **Tmax** | 0.67 hours (buffered formulation), 2 hours (delayed release capsules) |
| **Serum T ½** | 1.5h |
| **Intracellular T½** | 8-24h |
| **Drug Concentrations** | |
| **CSF (% of serum)** | 21%<br>2010 CNS Penetration Effectiveness (CPE) Score: 2 [Letendre S et al. 2010] |
| **Metabolism** | unclear % is liver or biliary; partly metabolized via hypoxanthine |
| **Excretion** | -30-50% renal excretion; likely active tubular secretion<br>- renal clearance 400ml/min<br>- clearance reduced 4-fold in uremia |

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| **Dosing – Adult** | > 60kg: 200 mg po q 12h (buffered tabs) or 400 mg once daily (EC caps or buffered tabs)<br>< 60kg: 125 mg po q 12h (buffered tabs) or 250 mg once daily (EC caps or buffered tabs)<br><br>Videx EC:<br>Take 1.5 hours before or 2 hours after food.<br><br>Videx Buffered Tablets:<br>Take 30 minutes before or 2 hours after food.<br>For ddI tablets, adults and children should receive 2 tablets/dose to prevent gastric degradation. Tablets should be chewed, manually crushed, or placed in 30mL H2O and stirred until dispersion formed, and drank within 1hr. For further flavoring, the aqueous dispersion can be further diluted with 30mL of clear apple juice; stir and drink immediately. If a one-tablet dose is given, it should be placed in 15mL H20 rather than 30mL, and can be flavored with 15mL clear apple juice. Tablets can also be mixed with chocolate milk and taken within 30 min. |
| **Dosing – Pediatric** | **Neonate** (< 90 days) (PACTG 239):<br>50 mg/m$^2$/dose po bid<br><br>**Pediatric dose (tablets)**[1] (>90 days): **120 mg/m$^2$/dose po q 12h**<br>Range: 90-150 mg/m$^2$/dose po q 12h<br>(Higher doses if risk of CNS disease, especially in young children with developmental delay.)<br><br>**Pediatric dose for EC formulation**:<br><br>The recommended total daily dose to be administered once daily to pediatric patients weighing at least 20 kg who can swallow capsules is based on body weight (kg), consistent with the recommended adult dosing guidelines:<br><br>Recommended Dosage (Adult and Pediatric Patients)<br>Body Weight — Dose<br>20 kg to less than 25 kg — 200 mg once daily<br>25 kg to less than 60 kg — 250 once daily<br>At least 60 kg — 400 mg once daily |

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| **Special instructions for pediatric patients** | 4 g bottle (product monograph revised 8/2014):<br>• Reconstitute with commercially available antacid that contains as active ingredients aluminum hydroxide (400 mg per 5 mL), magnesium hydroxide (400 mg per 5 mL), and simethicone (40 mg per 5 mL).<br>• If above strength not available, reconstitute with similar antacid of ½ strength using these alternative instructions: Add 400 mL of antacid in two, 200 mL portions, shaking the contents after each addition of 200 mL.<br>• Note: The admixture may be dispensed in flint-glass or plastic bottles.<br>• Didanosine oral solution contains antacids which may interfere with absorption of some medications if given at the same time.<br>• Combination of stavudine and didanosine is not recommended (unless benefits outweigh the risks) due to increased risk of serious toxicities.<br>Combination of didanosine and tenofovir should be avoided due to drug interaction and increased risk of pancreatitis. |
| **Adjust in Liver Dysfunction** | Single 400 mg dose, non-randomized, open label study performed in Child Pugh Class B (n=8), Class C (n=4) and healthy matched controls (n=12). Exposure to ddI slightly ↑ in hepatically impaired pts: GMR Cmax: 1.13 (0.70-1.82), GMR AUC 1.19 (0.87 –1.61). CLT/F not dependent on Child Pugh Score. Slight elevation in ddI exposures not considered clinically relevant (Chien et al. 2008).<br>No dose adjustment is needed, because a similar range and distribution of AUC and Cmax values was observed for subjects with hepatic impairment and matched controls. |
| **Adjust in Renal Failure/ Dialysis**<br>[a] CrCl (mL/min) for men:<br>(140 - age) (wt) x 60<br>(Scr) (50)<br><br>*CrCl (mL/min) for women:<br>as above multiplied by 0.85 | Reduce dose in renal impairment based on CrCl[a]:<br>Delayed release capsules (Videx EC):<br>• 30-59mL/min: 200mg QD (125 mg QD if <60 kg)<br>• 10-29 mL/min: 125mg QD (same dose if BW<60 kg)<br>• <10 mL/min: 125 mg QD (avoid if BW<60 kg)<br><br>Administer dose after hemodialysis; for CAPD dose as for CrCl <10mL/min |

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| **Toxicity** | diarrhea (common), abdominal pain , nausea, vomiting<br><br>peripheral neuropathy related to cumulative dose (12-34%)<br><br>asymptomatic hypertriglyceridemia/hyperamylasemia (10%), pancreatitis (1-7%) (use with caution or avoid use in alcoholics, hx of pancreatitis; avoid with d4T, ddC, hydroxyurea, ribavirin)<br><br>lactic acidosis and severe hepatomegaly with steatosis, including fatalities.<br><br>rare: liver failure, non-chirrotic portal hypertension [Maida et al. 2006, Kovari et al. 2009, Vispo et al. 2010], anemia, thrombocytopenia, hyperuricemia, hyperglycemia, , retinal depigmentation in pediatrics |
| **Pregnancy & Lactation** | Pregnancy risk category B.~50% placental transfer. No reported teratogenic effects in animals. Use standard adult dose. Cases of fatal lactic acidosis have been reported in pregnancy women on ddI with d4T- avoid combination. Use ddI only as alternate agent.ddI is secreted into breast milk of lactating rats |
| **Drug Interactions** | **Potential for additive/synergistic toxicity when coadministered with neurotoxins or pancreatoxins.**<br><br>In order to avoid absorption interactions, ddI tablets should be administered separately from **ketoconazole, itraconazole, indinavir, delavirdine, quinolones, tetracyclines, and ganciclovir**.<br><br>See separate Drug Interaction chart. |
| **Baseline Assessment** | CBC/diff, electrolytes, anion gap, serum bicarbonate, amylase, triglycerides, LFTs, urate, neurological status |
| **Routine Labs** | CBC/diff, electrolytes, anion gap, serum bicarbonate, amylase/lipase, LFTs q3-6mos<br>Measure serum lactate if low serum bicarbonate or high anion gap and Sx of lactic acidosis. Prodromal Sx include: nausea, anorexia, abdominal pain, vomiting, weight loss, fatigue. Rapidly progressive Sx: tachycardia, tachypnea, hyperventilation, dyspnea, muscular weakness, jaundice, mental status changes. May also progress to multi-organ failure (hepatic, pancreatitis, encephalopathy, respiratory) and death.<br><br>**D/C drug**: Sx of lactic acidosis, serum lactate > 5 mmol/L, amylase >200 (asymptomatic), pancreatitis, LFTs >5xULN, ANC< 0.5, plt <25000, gout, painful neuropathy |

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| **Dosage Forms** | **Enteric capsules (Videx EC)**:<br>125MG: DIN#02244596<br>200MG: DIN#02244597<br>250MG: DIN#02244598<br>400MG: DIN#02244599<br><br>**Pediatric Oral Powder for Solution**: 4g/240 mL bottle, DIN 01940635 (available via Special Access Program; call 514-333-2287)<br><br>**Generic** delayed release capsule approved in the U.S. (200 mg, 250 mg, and 400 mg capsules, Barr Laboratories). |
| **Storage** | Store all dosage forms at room temperature. Reconstituted oral powder should be stored in refrigerator x 30 days. |

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