

Selected Properties of Didanosine

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

Other names	Videx®, Videx EC®, ddI
Manufacturer	BristolMyersSquibb
Pharmacology/Mechanism of Action	<ul style="list-style-type: none"> • adenine analogue, intracellular triphosphorylation to active form with preferential activity in resting cells • causes viral DNA chain termination via absence of 3'-hydroxyl group to inhibit HIV reverse transcription • 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	<p>Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations):</p> <ul style="list-style-type: none"> • K65R, L74V • <i>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)</i> • <i>69 Insertion Complex is associated with resistance to all approved NRTIs when present with ≥1 TAM at codons 41, 210 or 215.</i> • <i>Q151M complex (with A62V, V75I, F77L, F116Y) is associated with resistance to all approved NRTIs except for tenofovir.</i>
Resistance - phenotypic	<p>Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/):</p> <p>K65R: 1.8-fold ↑ (intermediate resistance) L74V: 1.6-fold ↑ (intermediate resistance) L74V + M184V: 2.5-fold ↑ (intermediate resistance) M184V + TAMS: ↓ didanosine susceptibility</p>
Cross-Resistance	Cross-resistance to other nucleoside analogues possible.
Oral Bioavailability	<p>42%; susceptible to acid hydrolysis; food reduces absorption of buffered tablet by 50%</p> <ul style="list-style-type: none"> • high gastric pH rapidly achieved after oral dosing with buffered ddI tablets, but duration of elevated gastric pH was approx. 25 minutes (14-60)

Effect of Food	<p>Take on empty stomach.</p> <p>Buffered tablets require basic media for absorption (contains Al/Mg/Ca buffers).</p> <p>Delayed release capsules have ↓ C_{max} 46% and ↓ AUC 19% when taken with food compared to the fasting state. VIDEX EC should be taken on an empty stomach.</p>
Protein Binding	<5%
V_d	1.08L/kg
T_{max}	0.67 hours (buffered formulation), 2 hours (delayed release capsules)
Serum T_{1/2}	1.5h
Intracellular T_{1/2}	8-24h
Drug Concentrations	
CSF (% of serum)	21%
Metabolism	unclear % is liver or biliary; partly metabolized via hypoxanthine
Excretion	<p>-30-50% renal excretion; likely active tubular secretion</p> <p>- renal clearance 400ml/min</p> <p>- clearance reduced 4-fold in uremia</p>
Dosing – Adult	<p>> 60kg: 200 mg po q 12h (buffered tabs) or 400 mg once daily (EC caps or buffered tabs)</p> <p>< 60kg: 125 mg po q 12h (buffered tabs) or 250 mg once daily (EC caps or buffered tabs)</p> <p>Videx EC: Take 1.5 hours before or 2 hours after food.</p> <p>Videx Buffered Tablets: Take 30 minutes before or 2 hours after food. 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 H₂O 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.</p>

<p>Dosing – Pediatric</p>	<p>Neonate (< 90 days) (PACTG 239): 50 mg/m²/dose po bid</p> <p>Pediatric dose (tablets)¹ (>90 days): 120 mg/m²/dose po q 12h Range: 90-150 mg/m²/dose po q 12h (Higher doses if risk of CNS disease, especially in young children with developmental delay.)</p> <p>Pediatric dose for EC formulation: 240 mg/ m²/dose po once daily</p>
<p>Special instructions for pediatric patients</p>	<p>Note: Children need minimum of 2 tablets or use oral solution.</p> <ul style="list-style-type: none"> - chew tablets, crush or add 2 tablets to 30 mL cold water for 10 minutes, then stir, may then add 30 mL clear apple juice - do not give with other fruit juices or acidic drinks, feeds, or milk <p>Children may take ddI with food (one published study)</p> <p>Pediatric powder for oral solution also available. Final admixture concentration 10mg/mL. Shake well. Keep refrigerated x 30 days. Consult product monograph for reconstitution directions. Not suitable for once daily dosing.</p>
<p>Adjust in Liver Dysfunction</p>	<p>Manufacturer suggests reduce dose in moderate-severe hepatic dysfunction, but insufficient data to recommend specifics</p>
<p>Adjust in Renal Failure/ Dialysis</p> <p>^a CrCl (mL/min) for men: <u>(140 - age) (wt) x 60</u> (Scr) (50)</p> <p>*CrCl (mL/min) for women: as above multiplied by 0.85</p>	<p>Reduce dose in renal impairment based on CrCl^a:</p> <p>Delayed release capsules (Videx EC):</p> <ul style="list-style-type: none"> • 30-59mL/min: 200mg QD (125 mg QD if <60 kg) • 10-29 mL/min: 125mg QD (same dose if BW<60 kg) • <10 mL/min: 125 mg QD (avoid if BW<60 kg) <p>Buffered tablets (Videx):</p> <ul style="list-style-type: none"> • 30-59mL/min: 200mg QD (150 mg QD if <60 kg) • 10-29 mL/min: 150mg QD (100 mg QD if BW<60 kg) • <10 mL/min: 100 mg QD (75 mg QD if BW<60 kg) <p>NB: - the MgOH and AlOH buffers may be an excessive load in renal failure (see Availability/Cost for quantities) - administer dose after hemodialysis; for CAPD dose as for CrCl <10mL/min</p>

Toxicity	<p>diarrhea (common), abdominal pain , nausea ,, vomiting</p> <p>peripheral neuropathy related to cumulative dose (12-34%)</p> <p>asymptomatic hypertriglyceridemia/hyperamylasemia (10%), pancreatitis (1-7%) (use with caution or avoid use in alcoholics, hx of pancreatitis; avoid with d4T, ddC, hydroxyurea, ribavirin)</p> <p>lactic acidosis and severe hepatomegaly with steatosis, including fatalities.</p> <p>rare: liver failure, anemia, thrombocytopenia, hyperuricemia, hyperglycemia, , retinal depigmentation in pediatrics</p>
Pregnancy & Lactation	<p>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</p>
Drug Interactions	<p>Potential for additive/synergistic toxicity when coadministered with neurotoxins or pancreatoxins.</p> <p>In order to avoid absorption interactions, ddI tablets should be administered separately from ketoconazole, itraconazole, indinavir, delavirdine, quinolones, tetracyclines, and ganciclovir.</p> <p>See separate Drug Interaction chart.</p>
Baseline Assessment	<p>CBC/diff, electrolytes, anion gap, serum bicarbonate, amylase, triglycerides, LFTs, urate, neurological status</p>

<p>Routine Labs</p>	<p>CBC/diff, electrolytes, anion gap, serum bicarbonate, amylase/lipase, LFTs q3-6mos</p> <p>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.</p> <p>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</p>
<p>Dosage Forms</p>	<p>Enteric capsules (Videx EC):</p> <ol style="list-style-type: none"> 1. 125MG: DIN#02244596 2. 200MG: DIN#02244597 3. 250MG: DIN#02244598 4. 400MG: DIN#02244599 <p>Pediatric Oral Powder for Solution: 4g/240 mL bottle, DIN 01940635 (available via Special Access Program)</p> <p>Generic delayed release capsule approved in the U.S. (200 mg, 250 mg, and 400 mg capsules, Barr Laboratories).</p> <p>**buffered tablets discontinued in Canada as of February 2006</p> <p>Tablets: 25 & 50mg mint-flavored, 100 mg (DIN 01940546) & 150 mg (DIN 01940554) mandarin orange-flavored, chewable, dispersible</p> <p>25 & 50mg tabs contain 25.3mEq Mg hydroxide and 15.7mEq Al hydroxide; 100 & 150mg tabs contain 8mEq Mg hydroxide</p>
<p>Storage</p>	<p>Store all dosage forms at room temperature. Reconstituted oral powder should be stored in refrigerator x 30 days.</p>

References:

Bristol-Myers Squibb Canada. Videx & Videx EC Product Monographs. Montreal, QC:2004.