Selected Properties of Zalcitabine
product discontinued in Canada as of February 28, 2006

Other names	Hivid®, dideoxycytidine, ddC 
Manufacturer	Hoffmann La-Roche
Pharmacology/Mechanism of Action	• cytidine analogue, intracellular triphosphorylation to active form with preferential activity in resting cell • 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 laboratory and clinical isolates, the IC50 and IC95 values were in the range of 30-500 nM and 100-1000 nM, respectively (1 nM=0.21 ng/mL).
Resistance - genotypic	Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA 2004 Resistance Mutations): K65R, T69D, L74V, M184V *Presence of NAMS confers cross-resistance:* *M41L, E44D, D67N, K70R, V118I, L210W, T215Y/F, K219Q/E*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): K65R: intermediate levels of resistance to zalcitabine L74V: 2- to 5-fold ↓ susceptibility to zalcitabine M184V + TAMS: ↓ susceptibility to zalcitabine
Cross-Resistance	Point mutations at positions 65, 74, 75, and 184 are associated with resistance to didanosine, 75 with resistance to stavudine, and L65A and M184V with resistance to lamivudine.
Oral Bioavailability	>80% (CV 30%).70-87%; food reduces peak concentration 39% and reduces bioavailability 14%
Effect of Food	Best on empty stomach, but can take with food.
Protein Binding	<4%
Vd	0.5L/kg
Tmax	0.8 hours
Serum T ½	0.3-1.2h
Intracellular T½	2.6-10h
Drug Concentrations	After 1.5 mg oral dose (fasting), Cmax 25.2 ng/mL, AUC 72 ng.h/mL.
CSF (% of serum)	9-37% following IV (average 15-20%) 2010 CNS Penetration Effectiveness (CPE) Score: 1 [Letendre S et al. 2010]
Metabolism	unclear
Excretion	-62-75% excreted unchanged - renal clearance 190ml/min

Dosing – Adult	0.75mg TID
Dosing – Pediatric	Neonatal/Infant: unknown Pediatric: 0.01 mg/kg/dose po q8h Pediatric syrup only available as clinical investigational drug.
Special instructions for pediatric patients	If ddC upsets the stomach, take with food
Adjust in Liver Dysfunction	-may exacerbate pre-existing liver dysfunction; monitor for toxicity - may consider using 0.75 mg q8h in moderate-severe hepatic dysfunction
Adjust in Renal Failure/ Dialysis [a] CrCl (mL/min) for men: (140 - age) (wt) x 60 (Scr) (50) *CrCl (mL/min) for women: as above multiplied by 0.85	In patients with impaired renal function (Clcf <55 mL/min), zalcitabine half-life prolonged up to 8.5 hours. - reduce dose in renal impairment based on CrCl[a]: 10-40mL/min - 0.75mg q12h <10mL/min - 0.75mg q24h Dialysis: -insufficient data to recommend dose adjustment during dialysis (dose as per Clcr<10 mL/min); administer zalcitabine after completion of dialysis sessions
Toxicity	peripheral neuropathy related to cumulative dose (17-35%), oral ulcers (13%), h/a (8%), myalgias (5%), anemia (5%), leukopenia (9%), thrombocytopenia (4%), ↑ AST >250 (5%), rash (8%); lactic acidosis, mitochondrial toxicity reported rare: dysphagia, abdominal pain, pancreatitis, hepatomegaly
Pregnancy & Lactation	Pregnancy risk category C. 30-50% placental transfer in monkeys. Shown to be teratogenic in mice at exposure levels 1365 and 2730X max human AUC; in rats was teratogenic at exposure level 2142X human AUC, but not at 485X human AUC. No human studies. Due to terotogenicty in animals and lack of data, ddC is **not recommended** in pregnancy. -unknown whether ddC excreted into breast milk
Drug Interactions	**Potential for additive/synergistic toxicity when coadministered with neurotoxins or pancreatoxins.** **3TC** and ddC compete for intracellular phosphorylation in vitro, both cytidine analogues, thus avoid combination. Potential for similar antagonistic interaction with emtricitabine; avoid coadministration. See separate Drug Interaction chart.
Baseline Assessment	CBC/diff, electrolytes, anion gap, serum bicarbonate, amylase, LFTs, neurological status

Routine Labs	CBC/diff, electrolytes, anion gap, serum bicarbonate, amylase/lipase, LFTs q3-6mos 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. **D/C drug**: Sx of lactic acidosis, serum lactate > 5 mmol/L, amylase >200 (asymptomatic), pancreatitis, LFTs >5xULN, ANC< 0.5, plt <25000, painful neuropathy, oral ulceration
Dosage Forms	**Tablets:** 0.75mg grey, film-coated tablet, DIN 01990896; 0.375 mg tablet not available in Canada **Pediatric Syrup:** 0.1mg/mL (30mL)- available only as a clinical investigational drug. ***product discontinued in Canada as of February 28, 2006*
Storage	Store tablets at room temperature. Store syrup at room temperature in original glass bottle.

References:

Hoffmann-La Roche Limited. Hivid Product monograph. Mississauga, Ont.: 2004.

Letendre S, Ellis RJ, Deutsch R, Clifford DB, Collier AC, Gelman GG, et al. Correlates of time-to-loss-of-viral-response in CSF and plasma in the CHARTER Cohort: CPE score predicts CSF suppression [abstract 430]. 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 16-19, 2010.

