Selected Properties of Delavirdine

Other names	Rescriptor®
Manufacturer	ViiV Healthcare ULC
Pharmacology/Mechanism of Action	Bisheteroarypiperazine (BHAP) compound. Non-competitive, selective binding to reverse transcriptase enzyme causing conformational change that inactivates the catalytic site, preventing proviral DNA synthesis in HIV-1. Does not require intracellular phosphorylation.
Activity	In clinical isolates: mean IC50: 0.038 uM (0.001-0.69) IC90: 0.05-0.1 uM
Resistance - genotypic	Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations): **K103N***, ***V106M****, *Y181C*[#], **Y188L***, P236L ***multi-NNRTI resistance** [#]*accumulation of ≥2 leads to multi-NNRTI resistance*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): K103N: 34-fold ↑ (high resistance) V106A: 5-fold ↑ (intermediate resistance) Y181C/I: 24-fold ↑ (high resistance) Y188L: 10-fold ↑ (low resistance) P236L (rare mutation): 53-fold ↑ (high resistance) K103N +Y181C: 250-fold ↑ (high resistance)
Cross-Resistance	Rapid emergence of HIV strains that are cross-resistant to NNRTIs observed in vitro. Mutations at positions 103 and 181 have been associated with resistance to other NNRTIs. Cross-resistance between delavirdine and protease inhibitors or nucleoside analogues unlikely because enzyme targets are different.
Oral Bioavailability	85% (increased by approx. 20% if administered as slurry)
Effect of Food	Minimal food effect. Can take with or without food.
Protein Binding	98% (albumin)
Vd	
Tmax	1 hour
serum T ½	apparent plasma t1/2 increases with dose; mean t1/2 following 400 mg TID is 5.8 hours (range 2-11 hours)
Drug Concentrations	With 400 mg TID in HIV subjects (n=67): mean steady-state Cmax 35 ± 20 uM (range 2 to 100 uM), Cmin 15 ± 10 uM (range 0.1 to 45 uM), AUC 180 ± 100 uM.hr (range 5 to 515 uM • hr)

Minimum target trough concentrations (for wildtype virus)	
CSF (% of serum)	0.4% Steady-state delavirdine concentrations in saliva and semen were 6% and 2%, respectively, of corresponding plasma delavirdine concentrations. 2010 CNS Penetration Effectiveness (CPE) Score: 3 [Letendre S et al. 2010]
Metabolism	Metabolized via P450 3A4 oxidation, and 2D6 to a minor extent, followed by biliary excretion.
Excretion	44% of each dose excreted in feces. 5% renal excretion. Low renal clearance (<5mL/min).
Dosing – Adult	400mg TID 600 mg BID also being investigated. Can place 100 mg tablets (4 x 100 mg) in > 90 mL of water and wait for tablets to disintegrate, then stir to form suspension; this will increase the bioavailability 20%. The 200 mg tablets should be taken intact (USA only).
Dosing – Pediatric	Unknown
Special instructions for pediatric patients	Dissolve tablet in 30 mL water for a few minutes, stir and drink; rinse glass and drink again.
Adjust in Liver Dysfunction	Data not available. Use with caution in patients with impaired hepatic function.
Adjust in Renal Failure/Dialysis	Data not available, but no dosage adjustments likely required since delavirdine undergoes predominantly hepatic metabolism. Hemodialysis: administer after hemodialysis session, since hemodialysis removal of delavirdine has not been studied. CAPD: no dosage adjustment required.
Toxicity	**Rash:** mild rash +/- pruritus (35.4%), severe grade 3/4 rash (4.4%), SJS (0.1%). May be related to dose and blood levels. Can successfully continue drug in 85% if rash occurs, treat symptomatically with antihistamines, analgesics. **Discontinue** drug if severe rash or rash with constitutional symptoms (fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches, lymphadenopathy, increased LFTs or general malaise), and do not rechallenge. Rash typically occurs within first 4 wks of treatment. Avoid use of other NNRITs with history of severe rash to delavirdine. **Other, >5%:** nausea, vomiting, diarrhea, fatigue, headache, elevated LFTs.

Pregnancy & Lactation	Pregnancy category C drug. No adequate and well-controlled data in pregnant women. Excreted in the milk of lactating rats.
Drug Interactions	Delavirdine non-competetively inhibits P450 3A4. Also reduces CYP2C9 and CYP2C19 activity. See NNRTI interactions chart.
Baseline Assessment	CBC/diff, LFTs, examine skin for baseline.
Routine Labs	CBC/diff, LFTs q3-6mo. Assess for skin rash (most common in 1st 4 weeks of therapy). **D/C drug**: LFTs >5xULN, severe rash or rash with constitutional symptoms (see above under toxicity).
Dosage Forms	**100mg film-coated tablet** (DIN 02238348) 200 mg tablets available in the U.S.
Storage	Store at controlled room temperature 20° to 25 (6 8° to 77).

References:

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.

ViiV Healthcare ULC. Rescriptor Product Monograph. Montreal, QC: December 15, 2009.

