Selected Properties of Vicriviroc

**In October 2005, Schering Plough halted a phase II study of vicriviroc in treatment-naïve patients owing to early viral load rebound in the patients receiving the drug compared to control subjects receiving Combivir and efavirenz. A study in treatment-experienced patients is continuing.

**in January 2010, Merck announced that it would not attempt to obtain a license for vicriviroc in treatment-experienced patients with HIV following disappointing results in two phase III studies. Participants in the VICTOR E3 and E4 studies received an optimised background regimen determined by resistance testing to maximise the number of active drugs they received, and were randomised to receive vicriviroc or a placebo. However, in these studies, vicriviroc did not meet the primary efficacy endpoint. Merck will continue studies of vicriviroc in treatment-naïve patients. Vicriviroc is being tested as part of an innovative nucleoside-sparing regimen in combination with atazanavir/ritonavir.

***in July 2010, Merck announced that it was to halt all development of vicriviroc, following disappointing data from a phase II study of the drug in people with HIV with no previous history of treatment. The recently halted study in treatment-naïve patients was testing vicriviroc in combination with atazanavir/ritonavir as a nucleoside analogue-sparing regimen.

Other names	SCH417690
Manufacturer	Merck/Schering-Plough
Pharmacology/Mechanism of Action	CCR5 receptor antagonist (viral entry inhibitor) CCR5 antagonists target a discrete step in the viral entry pathway. The mechanism of HIV entry into the host CD4 T cells involves a sequence of molecular interactions between the virion envelope glycoprotein (Env) and host cell surface receptors. Normally, the gp120 Env subunit binds to CD4, and subsequent binding of HIV to the host cell's coreceptors (CCR5 or CXCR4) causes a conformational change leading to membrane fusion into the host cell. Allosteric binding of a CCR5 antagonist results in a receptor conformation that the virus cannot bind to, thus interfering with the fusion process.
Activity	Overall geometric mean IC_{50} of 0.61 nM and geometric mean IC_{90} of 6.0 nM
Resistance – genotypic	Data currently unavailable
Resistance – phenotypic	Data currently unavailable
Cross-Resistance	Data currently unavailable
Oral Bioavailability	Human data currently unavailable
Effect of Food	↓ rate of absorption and ↓ Cmax 58%, AUC not significantly affected by high-fat meal. Administer with or without food.[3]
Protein Binding	84% protein bound
Vd	Healthy volunteers: 620 – 807L HIV-1 infected patients: 778 – 960L
Tmax	1-2 hours

Serum T ½	>24 hours
Drug Concentrations	Pharmacokinetics of vicriviroc 5, 10 or 15 mg plus ritonavir are linear across all doses (Flexner et al. 2007). A significant and positive correlation between vicroviroc Cmin and AUC and viral load changes at week 2 in treatment-experienced patients has been observed (Flexner et al. 2007).
Minimum target trough concentrations (for wildtype virus)	In vitro IC90 3.9 ng/mL
CSF (% of serum)	Data currently unavailable
Metabolism	Metabolized by CYP3A4. Does not inhibit/induce CYP enzymes.
Excretion	5-15% excreted in urine
Dosing – Adult	Doses under investigation: 5-15 mg QD, 10-50 mg BID
Dosing – Pediatric	Data currently unavailable
Special instructions for pediatric patients	Data currently unavailable
Adjust in Liver Dysfunction	Data currently unavailable
Adjust in Renal Failure/Dialysis	In an open-label, randomized crossover study in subjects with hemodialysis dependent endstage renal disease (HD-ESRD), single doses of vicriviroc with or without ritonavir resulted in clinically insignificant changes in vicriviroc exposures compared to a matched control group with normal renal function. Vicriviroc AUC ↓ 16% when given alone in HD-ESRD vs. controls, while vicriviroc AUC ↑ 34% in HD-ESRD vs. controls when given with ritonavir.(Sansone-Parsons et al. 2007) Dose adjustment of vicriviroc is not necessary in renally impaired patients.
Toxicity	Headache (28%), nausea (14%), abdominal pain (12%), and pharyngitis (11%) Seizures in mice, rats, dogs and monkeys at high exposures. Vicriviroc with or without ritonavir, produces no clinically relevant cardiac or CNS changes in healthy subjects at exposures up to five times the expected dose to be used in HIV-infected patients in clinical practice [O'Mara et al. 2010]
Pregnancy & Lactation	Data currently unavailable

Drug Interactions	After concurrent dosing of healthy volunteers with vicriviroc 10mg daily and efavirenz 600mg daily for 14 days, vicriviroc Cmax and AUC were 67% and 81% lower versus when vicriviroc administered alone. When ritonavir was included with vicriviroc and efavirenz, vicriviroc Cmax and AUC were 196% and 384% higher than with vicriviroc administered alone. Ritonavir with vicriviroc alone resulted in vicriviroc Cmax and AUC of 278% and 582% higher than with vicriviroc alone. Lopinavir/ritonavir resulted in a 234% increase in Cmax and a 424% increase in AUC. The Cmax and AUC of lamivudine increased when given with vicriviroc; 85% and 96% respectively. The Cmax and AUC of zidovudine increased when given with vicriviroc; 92% and 93% respectively. See separate table on "Drug Interactions with CCR5 Inhibitors" for additional details.
Baseline Assessment	Data currently unavailable
Routine Labs	Data currently unavailable
Dosage Forms	White, round tablets available in 5-, 10-, and 25-mg strengths Green pentagonal tablets available in 10- and 15-mg strengths
Storage	White tablets stable for at least 36 months Green tablets stable for at least 18 months

References:

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