

Selected Properties of Maraviroc

Other names	UK-427,857, MVC, Selzentry
Manufacturer	Pfizer
Pharmacology/Mechanism of Action	<p>Maraviroc is a selective, slowly reversible, small molecule antagonist of the interaction between human CCR5 and HIV-1 gp120. Blocking this interaction prevents CCR5-tropic HIV-1 entry into cells.</p> <p>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.</p> <p>NB: Use of maraviroc is not recommended in patients with dual/mixed or CXCR4-tropic HIV-1 as efficacy was not demonstrated in a phase 2 study of this patient group.</p>

Activity	<p>The mean EC₅₀ value (50% effective concentration) for maraviroc against HIV-1 group M isolates (clades A to J) and group O isolates ranged from 0.1 to 1.25 nM (0.05 to 0.64 ng/mL) in cell culture. Mean potency against a range of CCR5-tropic clinical primary isolates: IC₉₀ 2.03 nM (1.04 ng/mL).</p> <p>In 973 treatment-experienced HIV-1-infected subjects in studies A4001027 and A4001028, the C_{min}, baseline viral load, baseline CD4, cell count and overall sensitivity score (OSS) were found to be important predictors of virologic success (defined as viral load < 400 copies/mL at 24 weeks).</p>
Resistance - genotypic	<p>HIV-1 variants with reduced susceptibility to maraviroc have been selected in cell culture. The maraviroc-resistant viruses remained CCR5-tropic with no evidence of a change from a CCR5-tropic virus to a CXCR4-using virus.</p> <p>Amino acid residue substitutions or deletions in the V3-loop region of the HIV-1 envelope glycoprotein (gp160) were found to be associated with maraviroc resistance. The relevance of the specific gp120 mutations observed in maraviroc-resistant isolates selected in cell culture to clinical maraviroc resistance is not known.</p>
Resistance - phenotypic	<p>Maraviroc-resistant viruses are characterized phenotypically by concentration response curves that do not reach 100% inhibition in phenotypic drug assays, rather than increases in EC₅₀ values.</p>
Cross-Resistance	<p>Maraviroc retains antiviral activity against HIV-1 clinical isolates resistant to NRTIs, NNRTIs, PIs and enfuvirtide in cell culture. Maraviroc-resistant viruses that emerged in cell culture remained susceptible to the fusion inhibitor enfuvirtide and the protease inhibitor saquinavir.</p>
Oral Bioavailability	<p>The absolute bioavailability of a 100 mg dose is 23% and is predicted to be 33% at 300 mg.</p>

Effect of Food	<p>Coadministration of a 300mg tablet with a high fat breakfast reduced maraviroc C_{max} and AUC by 33% in healthy volunteers. Coadministration of a high fat meal with 100 mg and 600 mg maraviroc reduced bioavailability by 43% and 25%, respectively (Chan et al. 2007).</p> <p>There were no food restrictions in the studies that demonstrated the efficacy and safety of maraviroc. Therefore, maraviroc can be taken with or without food at the recommended dose.</p>				
Protein Binding	Approximately 76% bound to human plasma proteins; maraviroc shows moderate affinity for albumin and alpha-1 acid glycoprotein.				
Vd	194 L				
Tmax	0.5-4 hours following single oral doses of 1-1200 mg administered to uninfected volunteers.				
serum T_{1/2}	terminal half life at steady state is 14-18 hours				
Drug Concentrations	The pharmacokinetics of oral maraviroc are not dose proportional over the dose range; estimated that doubling in dose will lead to 2.3-fold increase in mean AUC. In single-dose studies in humans, coefficients of variation of C _{max} and AUC were generally between 20-40%.				
	Maraviroc dose	N	AUC ₁₂ (ng·h/mL)	C _{max} (ng/mL)	C _{min} (ng/mL)
Healthy volunteers (phase 1)	300 mg twice daily	64	2908	888	43.1
Asymptomatic HIV patients (phase 2a)	300 mg twice daily	8	2550	618	33.6
Treatment-experienced HIV patients (phase 3)*	300 mg twice daily	94	1513	266	37.2
	150 mg twice daily (+ CYP3A inhibitor)	375	2463	332	101
* the estimated exposure is lower compared to other studies possibly due to food effect, compliance and concomitant medications.					
	Gender does not affect maraviroc concentrations. In a population pharmacokinetic model, average maraviroc AUC was 26.5% higher in Asian versus non-Asian subjects, a difference that does not require a dosage adjustment (Chan et al. 2007).				
Minimum target trough concentrations (for wildtype virus)	Currently no data available				
CSF (% of serum)	Currently no data available				

Metabolism	Metabolized by CYP3A4; P-glycoprotein substrate. Maraviroc does not inhibit activity of expressed enzymes (CYP1A2, CYP2C9, CYP2C19, or CYP3A4) in vitro up to 100uM. Weak inhibitor of CYP2D6 (IC ₅₀ 87uM). At supra-therapeutic concentrations, maraviroc is a weak inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 in human liver microsomes (IC ₅₀ > 30uM).	
Excretion	In the absence of metabolic inhibitors, renal clearance accounts for approximately 25% of total clearance of maraviroc.	
Dosing – Adult	<ul style="list-style-type: none"> • When given with strong CYP3A inhibitors (with or without CYP3A inducers) including: <ul style="list-style-type: none"> ○ PIs (except tipranavir/ritonavir) ○ delavirdine ○ ketoconazole, itraconazole, clarithromycin ○ other strong CYP3A inhibitors (e.g., nefazodone, telithromycin) 	150 mg BID
	<ul style="list-style-type: none"> • With NRTIs, tipranavir/ritonavir, nevirapine, and other drugs that are not strong CYP3A inhibitors or CYP3A inducers 	300 mg BID
	<ul style="list-style-type: none"> • With CYP3A inducers (without a strong CYP3A inhibitor) including: <ul style="list-style-type: none"> ○ efavirenz ○ rifampin ○ carbamazepine, phenobarbital, phenytoin 	600 mg BID
Dosing – Pediatric	There are no data available in pediatric patients; therefore maraviroc should not be used in patients <16 years of age.	
Special instructions for pediatric patients	Data currently not available	

<p>Adjust in Liver Dysfunction</p>	<p>The pharmacokinetics of single dose 300 mg maraviroc was studied in 3 groups of HIV-negative subjects: normal hepatic function, mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic impairment. Mean maraviroc AUC was ↑ 32% and ↑ 45% in subjects with mild and moderate hepatic impairment compared to subjects with normal hepatic function. Mean apparent oral clearance of maraviroc decreased with increasing hepatic impairment. Maraviroc was well tolerated in all study participants. (Abel et al. 2007).</p> <p>Caution advised in compromised hepatic function, including in patients with hepatitis B or C coinfection.</p>
<p>Adjust in Renal Failure/Dialysis</p>	<p>Data currently not available, therefore maraviroc should be used with caution in this population. In the absence of metabolic inhibitors, renal clearance accounts for approximately 25% of total clearance of maraviroc.</p> <p>Maraviroc concentrations may be increased in patients with renal impairment, especially when CYP3A inhibitors are coadministered. Patients with a creatinine clearance of less than 50 mL/min who receive maraviroc and a CYP3A inhibitor may be at an increased risk of adverse effects related to increased maraviroc concentrations, such as dizziness and postural hypotension. Thus, patients with a creatinine clearance of less than 50 mL/min should receive maraviroc and a CYP3A inhibitor only if the potential benefit is felt to outweigh the risk, and they should be monitored for adverse effects.</p>

<p>Toxicity</p>	<p>The most common adverse reactions (>8% incidence) which occurred at a higher frequency compared to placebo are cough, pyrexia, upper respiratory tract infections, rash, musculoskeletal symptoms, abdominal pain, and dizziness.</p> <p>Hepatotoxicity has been reported:</p> <ul style="list-style-type: none"> • May be preceded by evidence of a systemic allergic reaction (e.g., pruritic rash, eosinophilia or elevated IgE). • Immediately evaluate patients with signs or symptoms of hepatitis or allergic reaction. <p>Discontinuation of maraviroc should be considered in any patient with signs or symptoms of hepatitis, or with increased liver transaminases combined with rash or other systemic symptoms.</p> <p>Maraviroc antagonizes the CCR5 co-receptor located on some immune cells, and therefore could potentially increase the risk of developing infections. Patients should be monitored closely for evidence of infections while receiving maraviroc.</p> <p>Use with caution in the following patient populations:</p> <ul style="list-style-type: none"> ○ patients with pre-existing liver dysfunction or who are co-infected with viral hepatitis B or C ○ patients at increased risk for cardiovascular events ○ patients with a history of postural hypotension or on concomitant medication known to lower blood pressure
<p>Pregnancy & Lactation</p>	<p>Pregnancy category B. No apparent reproductive toxicity in rats at exposures significantly above maximal clinical dose. There are no adequate and well-controlled studies in pregnant women; therefore, safety for women of child-bearing age cannot be implied from available data.</p> <p>Studies in lactating rats indicate that maraviroc is extensively secreted into rat milk. It is not known whether maraviroc is secreted into human milk. Because of the potential for both HIV transmission and serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving maraviroc.</p>

Drug Interactions	<p>Maraviroc is a substrate of CYP3A and Pgp and hence its pharmacokinetics are likely to be modulated by inhibitors and inducers of these enzymes/transporters.</p> <p>CYP 3A4/P-glycoprotein inhibitors (ketoconazole, saquinavir, lopinavir/ritonavir, atazanavir, ritonavir) cause significant increases in systemic exposure of maraviroc ranging from 2- to 5-fold mean increases in Cmax and 3- to 10-fold mean increases in AUC.</p> <p>CYP 3A4/P-gp inducers (efavirenz, rifampicin) resulted in significant reduction in maraviroc systemic exposure ranging from 56-70% mean reduction in Cmax and AUC. This effect was similar in the presence and absence of CYP 3A4 inhibitors (lopinavir/r, saquinavir/r).</p> <p>Cotrimoxazole resulted in a decreased renal clearance of maraviroc.</p>
Baseline Assessment	Hepatic function (LFTs), BP, R5 tropism
Routine Labs	LFTs
Dosage Forms	150 mg and 300 mg blue film-coated tablets
Storage	Store tablets at room temperature between 15-30°C.

References:

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