Selected Properties of Maraviroc

Other names	UK-427,857, MVC, Celsentri®, Selzentry® (US)
Manufacturer	ViiV Healthcare ULC
Pharmacology/Mechanism of Action	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. 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. 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.
Activity	The mean EC_{50} 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: IC_{90} 2.03 nM (1.04 ng/mL). 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).
Resistance - genotypic	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. 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.
Resistance - phenotypic	Maraviroc-resistant viruses are characterized phenotypically by concentration response curves that do not reach 100% inhibition in phenotypic drug assays, rather than increases in EC_{50} values.

Cross-Resistance	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.
Oral Bioavailability	The absolute bioavailability of a 100 mg dose is 23% and is predicted to be 33% at 300 mg.
Effect of Food	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). 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.
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 ½	terminal half life at steady state is 14-18 hours
Drug Concentrations	The pharmacokinetics of oral maraviroc are <u>not</u> 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 Cmax 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). In 11 asymptomatic treatment-experienced HIV-positive patients without clinical evidence of STDs who were taking maraviroc for at least 4 weeks, the median maraviroc seminal plasma concentration was 197 ng/mL (15.8–1650 ng/mL), with all samples exceeding the median serum-adjusted EC90 of 0.57 ng/mL by several-fold, and the median maraviroc seminal plasma:blood plasma ratio was 0.89 (0.06–31.4).[Tiraboschi et al. 2010b]
Minimum target trough concentrations (for wildtype virus)	Suggested target of Caverage ≥75 ng/mL based on exposure-response analysis from the MERIT study.

CSF (% of serum)	Preclinical data in the rat indicate CSF exposure with concentrations ~10% of free plasma concentrations. In seven HIV-positive, virally suppressed patients receiving maraviroc as part of therapy, maraviroc concentrations were measured in paired CSF and plasma samples. Samples were obtained at median 10.5 h after dosing. Maraviroc was detectable in all samples, with median plasma concentration of 94.9 ng/mL (range 21.4–478.0) and median CSF level of 3.63 ng/mL (range 1.83-12.2). All CSF samples exceeded the median EC90 of 0.57 ng/mL. The median CSF/plasma ratio was 0.03 (range 0.01–0.10), and correlated significantly to time after sampling. CSF maraviroc concentrations did not correlate with plasma concentrations, CSF albumin, the CSF/plasma albumin ratio, or the CSF white blood cells.[Yilmaz et al. 2009] In 12 HIV-positive, treatment-experienced patients receiving maraviroc for at least a month, median MVC concentrations in plasma were 124.75 (7.3–517) ng/mL. All CSF concentrations were within the EC90 range (0.06-10.70) with the exception of one patient who was receiving an incorrect MVC dose with concomitant nevirapine. The median MVC CSF: plasma ratio was 0.022 (0.004–0.17), and when the free MVC plasma concentration was used, 0.094 (2.58–27.44). CSF viral load was <40 copies/mL in all 9 patients with undetectable plasma viral load.[Tiraboschi et al. 2010a] In six HIV-infected patients with neurological symptoms receiving cART including maraviroc, week 4 median plasma Ctrough was 347 (12-2678) ng/mL; CSF maraviroc was detectable in 4 patients with a median Ctrough of 102 (35-173) ng/mL, which is above the protein-adjusted IC90 of 0.57 ng/mL. Plasma and CSF viral loads decreased significantly in all patients.[Melica et al. 2010] 2010 CNS Penetration Effectiveness (CPE) Score: 3 [Letendre S et al. 2010]
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). Maraviroc could inhibit P-glycoprotein in the gut and may thus affect bioavailability of certain drugs; however, systemic effects of P-glycoprotein are unlikely to be clinically significant.
Excretion	In the absence of metabolic inhibitors, renal clearance accounts for approximately 25% of total clearance of maraviroc.

<table>
<tr><td rowspan="3">Dosing – Adult</td><td>• When given with strong CYP3A inhibitors (with or without CYP3A inducers) including:
o PIs (except tipranavir/ritonavir)
o delavirdine
o ketoconazole, itraconazole, clarithromycin
o other strong CYP3A inhibitors (e.g., nefazodone, telithromycin)</td><td>150 mg BID</td></tr>
<tr><td>• With NRTIs, tipranavir/ritonavir, nevirapine, and other drugs that are not strong CYP3A inhibitors or CYP3A inducers</td><td>300 mg BID</td></tr>
<tr><td>• With CYP3A inducers (without a strong CYP3A inhibitor) including:
o efavirenz, etravirine
o rifampin
o carbamazepine, phenobarbital, phenytoin</td><td>600 mg BID</td></tr>
<tr><td>Dosing – Pediatric</td><td colspan="2">In an ongoing open-label, dose finding and safety/efficacy, multi-center study, treatment-experienced HIV-infected children received maraviroc 40-450 mg BID with optimized background therapy (OBT). Participants were dosed initially according to body surface area and OBT based on interactions with maraviroc (adult-recommended doses with/without CYP3A4 inhibitors/inducers). Dose adjustment and PK re-evaluation occurred if average maraviroc concentrations (C_{avg}) at Week 2 were < 100 ng/mL. Of the 22 subjects taking maraviroc with a PI, only one failed to meet the PK target with the initial dose due to poor compliance. Conversely, all five subjects not receiving a potent CYP3A4 inhibitor (two nevirapine-based regimens; two raltegravir-based regimens; one NRTI-regimen) required at least doubling of the initial maraviroc dose.[Vourvahis et al. 2011]</td></tr>
<tr><td>Special instructions for pediatric patients</td><td colspan="2">Data currently not available</td></tr>
<tr><td>Adjust in Liver Dysfunction</td><td colspan="2">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).

Caution advised in compromised hepatic function, including in patients with hepatitis B or C coinfection.

Maraviroc concentrations are higher when a dose of 150 mg is administered with a strong CYP3A inhibitor compared to following administration of 300 mg without a CYP3A inhibitor, so patients with moderate hepatic impairment who receive maraviroc 150 mg with a strong CYP3A inhibitor should be monitored closely for maraviroc associated adverse events. Maraviroc has not been studied in subjects with severe hepatic</td></tr>
</table>

	impairment.
Adjust in Renal Failure/Dialysis	In the absence of metabolic inhibitors, renal clearance accounts for approximately 25% of total clearance of maraviroc. However, in the presence of metabolic inhibitors, renal clearance may account for up to 70% of total clearance of maraviroc, hence renal impairment may result in increased maraviroc exposures in this case. Therefore, maraviroc should be used with caution in patients with renal impairment (CLcr < 80ml/min) who are also taking potent CYP3A4 inhibitors. Recommended doses of maraviroc for patients with impaired renal function (CrCl ≤ 80 mL/min) are based on the results of a pharmacokinetic study conducted in healthy subjects with various degrees of renal impairment. The pharmacokinetics of maraviroc in subjects with mild and moderate renal impairment was similar to that in subjects with normal renal function. A limited number of subjects with mild and moderate renal impairment in the Phase 3 clinical trials (n= 131 and n= 12, respectively) received the same dose of maraviroc as that administered to subjects with normal renal function. In these subjects there was no apparent difference in the adverse event profile for maraviroc compared to subjects with normal renal function. **Patients with severe renal impairment (CrCl<30 mL/min) or end-stage renal disease (ESRD) and:** a) **NOT receiving a concomitant potent CYP3A inhibitor or inducer.** If such patients experience any symptoms of postural hypotension while taking maraviroc 300 mg twice daily, the dose should be reduced to 150 mg twice daily. **b) Co-treated WITH potent CYP3A4 inhibitors or inducers.** No studies have been performed in subjects with severe renal impairment (CrCl<30 mL/min) or ESRD co-treated with potent CYP3A4 inhibitors or inducers. Hence, no dose of maraviroc can be recommended, and **maraviroc is contraindicated for these patients.** Canadian Product Monograph dosing guidelines (March 2010): Table 9 provides dose interval adjustment guidelines based on simulations of increasing renal impairment in patients being co-administered potent CYP3A4 inhibitors. The safety and efficacy of these dose interval adjustments have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.

Table 9: Dose interval adjustments based on simulations of increasing renal impairment in patients being co-administered potent CYP3A4 inhibitors

Recommended CELSENTRI dose interval	Creatinine Clearance (CLcr) (ml/min)		
	50- 80 ml/min	30-50 ml/min	<30 ml/min
If co-administered without potent CYP3A4 inhibitors or coadministered with tipranivir/ritonavir	Every 12 hours	Every 12 hours	Every 12 hours
If co-administered with potent CYP3A4 inhibitors (e.g. PIs including lopinavir/ritonavir, darunavir/ritonavir, atazanavir/ritonavir (except tipranavir/ritonavir, saquinavir/ritonavir), ketoconazole, itraconazole, clarithromycin, telithromycin)	Every 24 hours	Every 24 hours	Every 24 hours
If co-administered with saquinavir/ritonavir	Every 24 hours	Every 48 hours	Every 72 hours

US Product Monograph dosing guidelines (May 2010):

Table 2 Recommended Dosing Regimens Based on Renal Function

Concomitant Medications*	SELZENTRY Dose Based on Renal Function				
	Normal	Mild	Moderate	Severe	End Stage Renal Disease (ESRD)
	CrCl >80 mL/min	CrCl >50 and ≤80 mL/min	CrCl ≥30 and ≤50 mL/min	CrCl <30 mL/min	On Regular Hemodialysis
Potent CYP3A inhibitors (with or without a CYP3A inducer)*	150 mg twice daily	150 mg twice daily	150 mg twice daily	NR	NR
Other concomitant medications*	300 mg twice daily	300 mg twice daily	300 mg twice daily	300 mg twice daily†	300 mg twice daily†
Potent CYP3A inducers (without a potent CYP3A inhibitor)*	600 mg twice daily	600 mg twice daily	600 mg twice daily	NR	NR

NR = not recommended
* See Table 1 for the list of concomitant medications.
† The SELZENTRY dose should be reduced to 150 mg twice daily if there are any symptoms of postural hypotension [see *Warnings and Precautions* (5.2)].

In subjects with ESRD, hemodialysis had minimal effect on maraviroc exposures. Therefore, maraviroc may be dosed without regard to dialysis.(Vourvahis et al. 2010)

Toxicity

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.

Hepatotoxicity has been reported:
• 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.
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.

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.

Use with caution in the following patient populations:
- o patients with pre-existing liver dysfunction or who are co-infected with viral hepatitis B or C
- o patients at increased risk for cardiovascular events
- o patients with a history of postural hypotension or on concomitant medication known to lower blood pressure

Pregnancy & Lactation	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. The pharmacokinetics of a single intrapartum dose of maraviroc was studied in pregnant rhesus macaques. Maraviroc was detected in the plasma of mothers up to 48 hours after dosing but only as long as 3.5 hours in the infants. The median fetal-maternal AUC-time curve ratio was 0.009 (range, 0.000 to 0.015). Maraviroc receptor occupancy data showed evidence of unprotected CCR5 receptors on $CD4^+$ cells in the mothers 24 to 48 hours after dosing. In summary, maraviroc was poorly transferred across the placenta and was quickly cleared from the infants' blood. The low concentrations of fetal maraviroc and short pharmacokinetic profile in infants suggest that a single maternal intrapartum dose of maraviroc would not be effective in reducing the risk of MTCT of HIV [Winters et al. 2010]. 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.**
Drug Interactions	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. CYP 3A4/P-glycoprotein inhibitors (ketoconazole, saquinavir, lopinavir/ritonavir, atazanavir, ritonovir) 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. 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). Cotrimoxazole resulted in a decreased renal clearance of maraviroc. Maraviroc does not induce CYP1A2 in vitro. In vitro results indicate that maraviroc could inhibit P-glycoprotein in the gut and may thus affect bioavailability of certain drugs. Maraviroc does not cause inhibition of CYP2D6 in vitro until concentrations > 100µM.
Baseline Assessment	Tropism testing, hepatic function (LFTs), blood pressure.
Routine Labs	LFTs
Dosage Forms	150 mg blue film-coated tablets, **DIN:** 02299844 300 mg blue film-coated tablets, **DIN:** 02299852

Storage	Store tablets at room temperature between 15-30^{o}C.

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