

## DRUG INTERACTIONS WITH CCR5 ANTAGONISTS

	<b>Maraviroc, MVC (Pfizer)</b>	<b>873140 (GSK)</b>	<b>417690, SCH-D (SCH)</b>
Doses under study	100-300 mg BID	400-600 mg BID	5-15 mg QD, 10-50 mg BID
Metabolism	3A4, Pgp	3A4, 2C19 (minor), weak 3A inhibitor <sup>1</sup> Substrate of P-glycoprotein.	CYP3A4
Food Effect	↓ ≤50% AUC	↑ 47-63% AUC <sup>2</sup>	
<b>Interactions with Antiretrovirals:</b>			
atazanavir	When maraviroc 300 mg BID was given with atazanavir 400 mg QD, maraviroc AUC ↑ 3.6-fold, Cmax ↑ 2.1-fold. Reduction of maraviroc dose by 50% in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended. <sup>3</sup>		
Atazanavir/ritonavir	When maraviroc 300 mg BID was given with atazanavir 300/ritonavir 100 mg QD, maraviroc AUC ↑ 4.9-fold, Cmax ↑ 2.7-fold. Reduction of maraviroc dose by 50% in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended. <sup>3</sup>		
AZT/3TC	In healthy volunteers, Combivir 1 tab BID + maraviroc 300 mg BID/placebo for 7 days showed no clinically relevant effect on the kinetics of AZT/3TC. <sup>4</sup>		In healthy volunteers, Combivir 1 tab BID + SCH-D 50 mg BID for 7 days showed no clinically relevant effect on the kinetics of AZT/3TC or of SCH-D. <sup>5</sup>
Efavirenz	When maraviroc 100 mg BID was given with efavirenz 600 mg QD,		In healthy adults, coadministration of efavirenz 600 mg

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	maraviroc AUC ↓ 50%, Cmax ↓ 60%. Doubling maraviroc dose to 200 mg BID corrected maraviroc exposures. When administering maraviroc with efavirenz (in the absence of protease inhibitors), doubling maraviroc dose is recommended. <sup>3</sup>		<p>QD and SCH-D 10 mg QD for 14 days resulted in 81% ↓ AUC, 67% ↓ Cmax of SCH-D vs. SCH-D alone.</p> <p>When SCH-D was given with <b>efavirenz plus ritonavir 100 mg QD</b>, SCH-D AUC ↑ 384%, Cmax ↑ 196% vs. SCH-D alone.<sup>6</sup></p>
Lopinavir/ritonavir	When maraviroc 100 mg BID was given with lopinavir/ritonavir 400/100 mg BID, maraviroc AUC ↑ 3.8-fold, Cmax ↑ 1.8-fold. Reduction of maraviroc dose to 50 mg BID resulted in maraviroc AUC ↑ 1.6-fold. Maraviroc 50% dose reduction in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended. <sup>3</sup>		<p>SCH-D exposure ↑ similarly by ritonavir or lopinavir/ritonavir:</p> <p>In healthy subjects, SCH-D 10 mg QD was given alone or with ritonavir 100 mg QD or lopinavir/ritonavir 400 mg QD for 14 days. In the presence of ritonavir, SCH AUC ↑ 5.4-fold and Cmax ↑ 2.5-fold, while in the presence of lopinavir/rtv, SCH AUC ↑ 4.2-fold and Cmax ↑ 2.3-fold. Both combinations were well tolerated.<sup>7</sup></p>
Nevirapine	In a cohort of HIV+ subjects (n=8) stabilized on nevirapine, 3TC and tenofovir, kinetics of single dose maraviroc 300 mg were unchanged vs. control		

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	data in HIV+ subjects receiving maraviroc alone for 10 days. <sup>8</sup>		
ritonavir	When maraviroc 100 mg BID was given with ritonavir 100 mg BID, maraviroc AUC ↑ 2.6-fold, Cmax ↑ 1.3-fold. Reduction of maraviroc dose to 50 mg BID gave similar exposures as maraviroc 100 mg BID alone. Maraviroc 50% dose reduction in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended. <sup>3</sup>		In healthy volunteers, ritonavir 100 mg QD or 100-400 mg BID plus SCH-D 10 mg BID significantly ↑ SCH AUC 500% (469-585%) and Cmax 350% (301-395%), regardless of ritonavir dose. <sup>9</sup>
saquinavir	When maraviroc 100 mg BID was given with saquinavir-sgc 1200 mg TID, maraviroc AUC ↑ 4.3-fold, Cmax ↑ 3.3-fold. Reduction of maraviroc dose by 50% in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended. <sup>3</sup>		
Saquinavir/ritonavir	When maraviroc 100 mg BID was given with saquinavir-sgc/ritonavir 1000/100 mg BID, maraviroc AUC ↑ 8.3-fold, Cmax ↑ 4.2-fold. Reduction of maraviroc dose to 25 mg BID resulted in maraviroc AUC ↑ 1.4-fold. Maraviroc 50% dose reduction in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended. <sup>3</sup>		
tenofovir	Maraviroc 300 mg BID did not affect kinetics of tenofovir 300 mg QD. <sup>3</sup>		In healthy volunteers, tenofovir 300 mg QD plus

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			SCH-D 10 mg BID for 7 days showed no clinically relevant effect on the kinetics of either drug. Tenofovir was given with the morning SCH dose with food. <sup>10</sup>
<b>Multi-ARV drug interactions:</b>			
Efavirenz plus lopinavir/ritonavir	<p>Efavirenz approximately halves the boosting effect of PIs on maraviroc exposure.</p> <p>When maraviroc 300 mg BID was given with lopinavir/ritonavir 400/100 mg BID plus efavirenz 600 mg QD, maraviroc AUC ↑ 2.5-fold, C<sub>max</sub> ↑ 1.3-fold vs. maraviroc alone.</p> <p>Recommendations on dose adjustments currently not available (maraviroc efficacy driven by AUC, while adverse events likely related to C<sub>max</sub>).<sup>3</sup></p>		
Efavirenz plus saquinavir/ritonavir	<p>Efavirenz approximately halves the boosting effect of PIs on maraviroc exposure.</p> <p>When maraviroc 100 mg BID was given with saquinavir-sgc/ritonavir 1000/100 mg BID plus efavirenz 600 mg QD, maraviroc AUC ↑ 5-fold, C<sub>max</sub> ↑ 2.3-fold vs. maraviroc alone.</p> <p>Recommendations on dose adjustments currently not</p>		

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	available (maraviroc efficacy driven by AUC, while adverse events likely related to Cmax). <sup>3</sup>		
<b>Interactions with other medications:</b>			
Oral contraceptives	Maraviroc 100 mg BID had no effect on exposure of ethinylestradiol 30ug/levonorgestrel 150ug QD. <sup>3</sup>		
Ketoconazole	When given with ketoconazole 400 mg QD, maraviroc AUC ↑ 5-fold, Cmax ↑ 3.4-fold. Reduction of maraviroc dose by 50% in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended. <sup>3</sup>		
Midazolam	Maraviroc 300 mg BID had no effect on single-dose exposure of midazolam 7.5 mg. <sup>3</sup>		
rifampin	When maraviroc 100 mg BID was given with rifampin 600 mg QD, maraviroc AUC and Cmax ↓ 70%. Doubling maraviroc dose to 200 mg BID corrected maraviroc exposures. When administering maraviroc with rifampin, doubling maraviroc dose is recommended. <sup>3</sup>		
trimethoprim	Maraviroc 300 mg BID did not affect kinetics of trimethoprim 960 mg BID. <sup>3</sup>		

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