

## DRUG INTERACTIONS WITH CCR5 ANTAGONISTS

	<b>Maraviroc, MVC, Selzentry® (Pfizer)</b>	<b>Aplaviroc (GSK)</b>	<b>Vicriviroc (SCH)</b>
Doses under study	150-600 mg BID, depending on concomitant medications	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	↓ 33% AUC with high fat meal	↑ 47-63% AUC <sup>2</sup>	↓ rate of absorption and ↓ Cmax 58%, AUC not significantly affected by high-fat meal. Administer with or without food. <sup>3</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, Cmin ↑ 4.2-fold. Reduction of maraviroc dose by 50% in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended. <sup>4</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, Cmin ↑ 6.7-fold. Reduction of maraviroc dose by 50% in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended. <sup>4</sup>	Combination of aplaviroc 400 mg BID or 800 mg QD plus atazanavir 300 mg/ritonavir 100 mg QD in healthy volunteers resulted in significant increases in aplaviroc exposures (7-13 fold ↑ AUC, 2-5 fold ↑ Cτ,) with a greater effect when aplaviroc was dosed QD. Atazanavir kinetics	The combination of vicriviroc 15 mg/ritonavir 100 mg QD plus atazanavir 300 mg QD in healthy volunteers did not lead to significant changes in vicriviroc plasma levels, compared to vicriviroc 15 mg QD /ritonavir 100 mg BID alone. Vicriviroc may be added to a ritonavir-

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		were not significantly changed in the presence of aplaviroc. <sup>5</sup>	boosted PI regimen without dosage adjustment. <sup>6</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>7</sup>		In healthy volunteers, Combivir 1 tab BID + vicriviroc 50 mg BID for 7 days showed no clinically relevant effect on the kinetics of AZT/3TC or of vicriviroc. <sup>8</sup>
Darunavir/ritonavir	In healthy subjects, <b>maraviroc 150 mg BID plus darunavir 600/ritonavir 100 mg BID</b> resulted in 2.3-fold ↑ C <sub>max</sub> , 4-fold ↑ AUC of maraviroc vs. maraviroc administered alone. Reduce maraviroc dose to 150 mg BID when coadministering with darunavir/ ritonavir. <sup>9</sup>  See additional entry for <b>darunavir/ritonavir + etravirine plus maraviroc.</b>		
Efavirenz	When maraviroc 100 mg BID was given with efavirenz 600 mg QD, maraviroc AUC ↓ 50%, C <sub>max</sub> ↓ 60%, C <sub>min</sub> ↓ 45%. Doubling maraviroc dose to 200 mg BID corrected maraviroc exposures.  <b>When administering maraviroc with efavirenz (in the absence of protease inhibitors),</b>	In healthy adults, coadministration of aplaviroc 600 mg BID and efavirenz 600 mg QD for 10 days led to 57% ↓ AUC and 61% ↓ C <sub>t</sub> of aplaviroc. Efavirenz exposures were not significantly different compared to historical controls. <sup>10</sup> Co-administration with a boosted PI	In healthy adults, coadministration of efavirenz 600 mg QD and vicriviroc 10 mg QD for 14 days resulted in 81% ↓ AUC, 67% ↓ C <sub>max</sub> of vicriviroc vs. vicriviroc alone.  When vicriviroc was given with <b>efavirenz plus ritonavir 100 mg QD</b> , vicriviroc

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	<b>doubling maraviroc dose is recommended.</b> <sup>4</sup>	regimen (e.g., FPV/rtv 700/100 mg BID) may be effective in counter-acting the inductive effects of EFV. <sup>11</sup>	AUC ↑ 384%, Cmax ↑ 196% vs. vicriviroc alone. <sup>12</sup>
Elvitegravir/ ritonavir	In a randomized, healthy subject study (n=28), volunteers received EVG/r 150/100mg QD for 10 days followed by EVG 150/100mg QD plus maraviroc 150mg BID for 10 days or vice versa. No clinically relevant changes in EVG/rtv kinetics were observed with the combination, while maraviroc exposures were ↑ in the presence of EVG/rtv (maraviroc AUC ↑ 2.15 fold, Cmax ↑ 2.86 fold). Therefore, <b>reduce maraviroc dose to 150mg BID when used with EVG/r</b> (same as dose recommendation for MVC + other CYP 3A4 inhibitors). <sup>13</sup>		
Etravirine	Total maraviroc concentrations over a 12-hour period are reduced by 53% (AUC <sub>12</sub> ) and peak levels of maraviroc (C <sub>max</sub> ) by 60% in the presence of etravirine.  Therefore, if a patient isn't also taking a potent CYP3A4 inhibitors such as a protease inhibitor, <b>maraviroc dose should be increased to 600mg twice</b>		

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	<p><b>daily.</b> No dose adjustment of etravirine is required.</p> <p>See additional entry for <b>darunavir/ritonavir + etravirine plus maraviroc.</b></p>		
Fosamprenavir/ritonavir			<p>The combination of vicriviroc 15 mg QD plus fosamprenavir 700 mg/ritonavir 100 mg BID in healthy volunteers did not lead to significant changes in vicriviroc plasma levels, compared to vicriviroc 15 mg QD/ritonavir 100 mg BID alone.</p> <p>Vicriviroc may be added to a ritonavir-boosted PI regimen without dosage adjustment.<sup>6</sup></p>
Indinavir/ritonavir			<p>The combination of vicriviroc 15 mg QD plus indinavir 800 mg/ritonavir 100 mg BID in healthy volunteers did not lead to significant changes in vicriviroc plasma levels, compared to vicriviroc 15 mg QD/ritonavir 100 mg BID alone.</p> <p>Vicriviroc may be added to a ritonavir-boosted PI regimen without dosage adjustment.<sup>6</sup></p>
Lamivudine	Maraviroc had no effect on		

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	the pharmacokinetics of lamivudine. <sup>14</sup>		
Lopinavir/ritonavir	<p>When maraviroc 100 mg BID was given with lopinavir/ritonavir 400/100 mg BID, maraviroc AUC ↑ 3.8-fold, C<sub>max</sub> ↑ 1.8-fold, C<sub>min</sub> ↑ 9.2-fold. Reduction of maraviroc dose to 50 mg BID resulted in maraviroc AUC ↑ 1.6-fold.</p> <p><b>Maraviroc 50% dose reduction in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.</b><sup>4</sup></p>		<p>Vicriviroc exposure ↑ similarly by ritonavir or lopinavir/ritonavir:</p> <p>In healthy subjects, vicriviroc 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, vicriviroc AUC ↑ 5.4-fold and C<sub>max</sub> ↑ 2.5-fold, while in the presence of lopinavir/rtv, vicriviroc AUC ↑ 4.2-fold and C<sub>max</sub> ↑ 2.3-fold. Both combinations were well tolerated.<sup>15</sup></p>
nelfinavir			<p>The combination of vicriviroc 15 mg QD /ritonavir 100 mg BID plus nelfinavir 1250 mg BID in healthy volunteers did not lead to significant changes in vicriviroc plasma levels, compared to vicriviroc 15 mg QD /ritonavir 100 mg BID alone. Vicriviroc may be added to a ritonavir-boosted PI regimen without dosage adjustment.<sup>6</sup></p>

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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 data in HIV+ subjects receiving maraviroc alone for 10 days. <sup>16</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>4</sup>		In healthy volunteers, ritonavir 100 mg QD or 100-400 mg BID plus vicriviroc 10 mg BID significantly ↑ SCH AUC 500% (469-585%) and Cmax 350% (301-395%), regardless of ritonavir dose. <sup>17</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>4</sup>		
Saquinavir/ritonavir	When maraviroc 100 mg BID was given with saquinavir-sgc/ritonavir 1000/100 mg BID, maraviroc AUC ↑ 9.8-fold, Cmax ↑ 4.8-fold. Reduction of maraviroc dose to 25 mg BID resulted in maraviroc AUC ↑ 1.4-		The combination of vicriviroc 15 mg QD plus saquinavir-sgc 1000 mg/ritonavir 100 mg BID in healthy volunteers did not lead to significant changes in vicriviroc plasma

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	fold. Maraviroc 50% dose reduction in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended. <sup>14</sup>		levels, compared to vicriviroc 15 mg QD/ritonavir 100 mg BID alone. Vicriviroc may be added to a ritonavir-boosted PI regimen without dosage adjustment. <sup>6</sup>
tenofovir	Maraviroc 300 mg BID did not affect kinetics of tenofovir 300 mg QD. <sup>4</sup>	Healthy volunteer, randomized study of tenofovir 300 mg daily and aplaviroc 600 mg BID showed no significant effect of tenofovir on aplaviroc AUC or C <sub>max</sub> , and a moderate increase in C <sub>τ</sub> of 80%. Tenofovir pharmacokinetics were not changed in the presence of aplaviroc. <sup>18</sup>	In healthy volunteers, tenofovir 300 mg QD plus vicriviroc 10 mg BID for 7 days showed no clinically relevant effect on the kinetics of either drug. Tenofovir was given with the morning vicriviroc dose with food. <sup>19</sup>
Tipranavir/ ritonavir	Combination of maraviroc 150 mg BID plus tipranavir 500/200 mg BID in healthy subjects did not lead to any significant changes in maraviroc exposures. <sup>20</sup>		Vicriviroc 15 mg QD was administered with ritonavir 200 mg BID or with tipranavir 500 mg/ritonavir 200 mg BID in healthy subjects. When compared to VCV values with RTV alone, the addition of tipranavir did not significantly alter VCV exposure. Vicriviroc dose adjustment is not required when co-administering with

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			tipranavir/ ritonavir. <sup>21</sup>
Zidovudine	Maraviroc had no effect on the pharmacokinetics of zidovudine. <sup>14</sup>		
<b>Multi-ARV drug interactions:</b>			
Darunavir/ritonavir + etravirine	Co-administration of <b>etravirine/darunavir/ritonavir</b> with maraviroc increased the exposure of maraviroc by 210% (AUC <sub>12</sub> ) and peak levels (C <sub>max</sub> ) by 77% compared to maraviroc alone.  Thus, if maraviroc is being dosed alongside etravirine and darunavir together, a dose reduction to 150mg twice daily is necessary.		
Efavirenz plus fosamprenavir/ritonavir		Co-administration of aplaviroc 400 mg BID, fosamprenavir 700 mg/ritonavir 100 mg BID and efavirenz 600 mg QD led to a 2.6-fold ↑ AUC and 2.5-fold ↑ Ctau of aplaviroc compared to aplaviroc alone. <sup>11</sup>  Therefore, co-administration with a boosted PI regimen appears to be effective in counter-acting the inductive effects of EFV.	
Efavirenz plus lopinavir/ritonavir	When maraviroc 300 mg BID was given with lopinavir/ritonavir		

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	400/100 mg BID plus efavirenz 600 mg QD, maraviroc AUC ↑ 2.5-fold, C <sub>max</sub> ↑ 1.3-fold, C <sub>min</sub> ↑ 6.3-fold vs. maraviroc alone. <sup>14</sup>  Maraviroc 150 mg BID dose recommended. <sup>14</sup>		
Efavirenz plus saquinavir/ritonavir	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, C <sub>min</sub> ↑ 8.4-fold vs. maraviroc alone. <sup>14</sup>  Maraviroc 150 mg BID dose recommended. <sup>14</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>4</sup>		
Ketoconazole	When given with ketoconazole 400 mg QD, maraviroc AUC ↑ 5-fold, C <sub>max</sub> ↑ 3.4-fold. Reduction of maraviroc dose by 50% in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended. <sup>4</sup>		
Midazolam	Maraviroc 300 mg BID had no effect on single-dose exposure of midazolam 7.5 mg. <sup>4</sup>		
rifampin	When maraviroc 100 mg BID was given with		

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	rifampin 600 mg QD, maraviroc AUC and Cmax ↓ 70%, Cmin ↓ 78%. Doubling maraviroc dose to 200 mg BID corrected maraviroc exposures. When administering maraviroc with rifampin, doubling maraviroc dose is recommended. <sup>4</sup>		
trimethoprim	Maraviroc 300 mg BID did not affect kinetics of trimethoprim 960 mg BID. <sup>4</sup>		

### References:

1. Johnson B, Song I, Adkinson K, Borland J, Fang L, Lou Y, et al. 873140, a novel CCR5 receptor antagonist, does not significantly interact with major drug metabolizing enzymes [abstract 75]. 6th International Workshop on Clinical Pharmacology of HIV Therapy, Quebec. April 28-30, 2005.
2. Adkinson K, Song I, Fang L, Bernstein J, Shachoy-Clark A, Lou Y, et al. The effect of food and formulation on the pharmacokinetics of the novel CCR5 antagonist, 873140 [abstract 81]. 6th International Workshop on Clinical Pharmacology of HIV Therapy, Quebec. April 28-30, 2005.
3. Keung A, Sansone A, Caceres M, Kraan M, Gaillac B. Effect of Food on Bioavailability of SCH 417690 in Healthy Volunteers [abstract A-1200]. 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC. December 16-19, 2005.
4. Abel S, Russell D, Ridgway C, Muirhead G. Overview of the drug-drug interaction data for maraviroc (UK-427,857) [abstract 76]. 6th International Workshop on Clinical Pharmacology of HIV Therapy, Quebec. April 28-30, 2005.
5. Song I, Adkison K, Shachoy-Clark A, Pritchard J, Fang L, Lou Y, et al. Pharmacokinetic interaction between 873140 and atazanavir/ritonavir [abstract A-1196]. 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC. December 16-19, 2005.
6. Sansone A, Keung A, Tetteh E, Weisbrot H, Martinho M, Lang S, et al. Pharmacokinetics of vicriviroc are not affected in combination with five different protease inhibitors boosted by ritonavir [abstract 582]. 13th Conference on Retroviruses and Opportunistic Infections, Denver, CO. February 5-8, 2006.
7. Russell D, Abel S, Hackman F, Whitlock L, Van der Merwe R, Muirhead G. The effect of maraviroc (UK-427,857) on the pharmacokinetics of 3TC/AZT (Combivir) in healthy subjects [abstract 30]. 6th International Workshop on Clinical Pharmacology of HIV Therapy, Quebec. April 28-30, 2005:21.
8. Sansone A, Guillaume M, Kraan M, Keung A, Caceres M, Boutros T. The pharmacokinetics of SCH 417690 when administered alone and in combination with

- lamivudine/zidovudine [abstract 84]. 6th International Workshop on Clinical Pharmacology of HIV Therapy, Quebec. April 28-30, 2005.
9. Abel S, Ridgway C, Hamlin J, al. E. An open, randomised, 2-way crossover study to investigate the effect of darunavir/ritonavir on the pharmacokinetics of maraviroc in healthy subjects [abstract 55]. 8th International Workshop on Pharmacology of HIV Therapy, Budapest, Hungary. April 16-18, 2007.
  10. Adkison K, Fang L, Shachoy-Clark A, Lou Y, Otto V, Berrey MM, et al. The pharmacokinetic interaction between the entry inhibitor 873140 and efavirenz in healthy adults [abstract A-1197]. 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC. December 16-19, 2005.
  11. Adkison K, Fang L, Shachoy-Clark A, Lou Y, Min S, Otto V, et al. Coadministration of fosamprenavir/ritonavir overcomes the effect of efavirenz induction on 873140 pharmacokinetics [abstract A-1194]. 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC. December 16-19, 2005.
  12. Sansone A, Saltzman M, Rosenberg M, Kraan M, Soni P, Keung A, et al. Pharmacokinetics of SCH 417690 administered alone or with ritonavir and efavirenz in healthy volunteers [abstract 79]. 6th International Workshop on Clinical Pharmacology of HIV Therapy, Quebec. April 28-30, 2005.
  13. Ramanathan S, West S, Abel S, Enejosa J, Kearney BP. Pharmacokinetics of coadministered ritonavir-boosted elvitegravir plus maraviroc [abstract H-1050]. 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL. September 17-20, 2007.
  14. Pfizer Labs. SELZENTRY (maraviroc) Prescribing Information. New York, NY: August 2007
  15. Sansone A, Saltzman M, Rosenberg M, Kraan M, Keung A, Boutros T. Pharmacokinetics of SCH 417690 administered alone or in combination with ritonavir or lopinavir/ritonavir [abstract 83]. 6th International Workshop on Clinical Pharmacology of HIV Therapy, Quebec. April 28-30, 2005.
  16. Muirhead G, Russell D, Pozniak A, Boffito M, Moyle GJ, Gazzard B, et al. A novel probe drug interaction study to investigate the effect of selected ARV combinations on the PK of a single oral dose of Maraviroc in HIV+ve subjects [abstract 31]. 6th International Workshop on Clinical Pharmacology of HIV Therapy, Quebec. April 28-30, 2005.
  17. Sansone A, Seiberling M, Kraan M, Keung A, Martinho M. Similar increase in SCH 417690 exposure with coadministration of varying doses of ritonavir in healthy volunteers [abstract 78]. 6th International Workshop on Clinical Pharmacology of HIV Therapy, Quebec City. April 28-30, 2005.
  18. Song I, Adkison K, Shachoy-Clark A, Fang L, Lou Y, Otto V, et al. Absence of pharmacokinetic drug interaction between 873140 and tenofovir disoproxil fumarate [abstract A-1195]. 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC. December 16-19, 2005.
  19. Sansone A, Guillaume M, Kraan M, Soni P, Keung A, Boutros T. Pharmacokinetics of SCH 417690 administered alone or in combination with tenofovir [abstract 85]. 6th International Workshop on Clinical Pharmacology of HIV Therapy, Quebec City. April 28-30, 2005.

20. Abel S, al. E. Effect of boosted tipranavir on the pharmacokinetics of maraviroc (UK 427,857) in healthy volunteers [abstract LBPE4.3/15]. 10th European AIDS Conference, Dublin. November 17-20, 2005.
21. Sansone-Parsons A, al. E. The addition of tipranavir has no impact on the pharmacokinetics of vicriviroc when coadministered with a potent CYP3A4 inhibitor such as ritonavir [abstract 57]. 8th International Workshop on Clinical Pharmacology of HIV Therapy, Budapest, Hungary. April 16-18, 2007.