

## Selected Properties of APlaviroc

\*\*\*Aplaviroc entered Phase 3 development in July 2005 for the treatment of HIV-1 infection in treatment-experienced patients. In September 2005, GSK terminated all Phase 2b clinical trials in HIV treatment-naïve patients, as well as studies in healthy volunteers, due to cases of severe hepatotoxicity. In October 2005, GSK terminated all Phase 3 studies in treatment-experienced patients with multi-drug resistant virus and limited treatment options, due to a case report of elevated LFTs and bilirubin in one patient. No further clinical studies with aplaviroc are being planned.

<b>Other names</b>	GSK 873140
<b>Manufacturer</b>	GlaxoSmithKline
<b>Pharmacology/Mechanism of Action</b>	<p>CCR5 receptor antagonist (viral entry inhibitor)</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>
<b>Activity</b>	<p>Aplaviroc has potent in vitro antiviral activity, with a 50% inhibitory concentration (IC<sub>50</sub>) against CCR5-tropic HIV type 1 (HIV-1) in the subnanomolar range. Aplaviroc selectively inhibits MIP1<math>\alpha</math> and MIP1<math>\beta</math> binding in the 2 to 10 nM range and does not cause internalization of the receptor.</p> <p>In vitro studies suggest potential synergy among entry inhibitors.</p>
<b>Resistance - genotypic</b>	
<b>Resistance - phenotypic</b>	
<b>Cross-Resistance</b>	
<b>Oral Bioavailability</b>	3-30% (animal data)
<b>Effect of Food</b>	<p>Food consumption of a high fat meal (869 cal; 53% fat, 32.1 g protein, 70.2 g carbohydrate, and 51.1 g fat) increased the AUC and C<sub>max</sub> by a mean of 1.7- and 2.2-fold, respectively.</p>

<b>Protein Binding</b>	93% in human plasma
<b>Vd</b>	
<b>Tmax</b>	1.75-5 hours
<b>serum T<sub>1/2</sub></b>	Rapid terminal elimination half-life of 0.4 to 1.6 hours. However, the half-life of dissociation from the receptor exceeds 150 hours in vitro.
<b>Drug Concentrations</b>	<p>With 200 mg BID: median AUC 127 ng · h/ml, C<sub>max</sub> 24 ng/ml</p> <p>With 800 mg BID: median AUC 329 ng · h/ml, C<sub>max</sub> 100 ng/ml. Steady-state C<sub>trough</sub> reached by day 5.</p> <p>With repeat dose escalation, the increase in C<sub>max</sub> is dose proportional, whereas the increase in AUC(0-12) and C<sub>12</sub> values tend to be less than dose proportional. Accumulation is greater at lower vs. higher doses.</p> <p>High intersubject variability in AUC and C<sub>max</sub> observed, with greater variability seen with higher vs. lower doses and single vs. repeat doses. Intersubject variability in AUC and C<sub>max</sub> not improved when drug administered with food, suggesting that first-pass metabolism rather than gastrointestinal absorption may be the main source of variability.</p>
<b>Minimum target trough concentrations (for wildtype virus)</b>	<p>Plasma concentrations above the protein binding corrected the IC<sub>90</sub> (~24 ng/ml, estimated as four times the IC<sub>50</sub> in peripheral blood mononuclear cells), suggesting that therapeutic concentrations can be achieved with oral doses of ≥200 mg BID.</p> <p>The specific aplaviroc pharmacokinetic parameter that best predicts antiviral activity remains to be determined. The activity of aplaviroc and other compounds in the CCR5 class may be a function of prolonged receptor binding. Therefore, the antiviral activity of durably bound CCR5 antagonists may be more closely related to C<sub>max</sub> or AUC than trough concentrations.</p>
<b>CSF (% of serum)</b>	
<b>Metabolism</b>	Extensively metabolized to multiple oxidative and glucuronide metabolites (animal data). Predominately metabolized by CYP3A4, 2C19 (minor), weak 3A inhibitor. <sup>1</sup> Substrate of P-glycoprotein.

<b>Excretion</b>	Moderate clearance (averaging ~50% of liver blood flow) based on data from single dose IV administration in rats and monkeys.
<b>Dosing – Adult</b>	Doses under study: 200-400 mg BID or 800 mg QD with a meal
<b>Dosing – Pediatric</b>	
<b>Special instructions for pediatric patients</b>	
<b>Adjust in Liver Dysfunction</b>	
<b>Adjust in Renal Failure/Dialysis</b>	
<b>Toxicity</b>	Primarily upper and lower gastrointestinal symptoms, e.g., loose stools, diarrhea, headache, dizziness, abdominal pain, and nausea.
<b>Pregnancy &amp; Lactation</b>	
<b>Drug Interactions</b>	See separate Drug Interaction table.
<b>Baseline Assessment</b>	
<b>Routine Labs</b>	
<b>Dosage Forms</b>	200 mg round, white tablets
<b>Storage</b>	

**References:**

Adkinson KK, Shachoy-Clark A, Fang L, Lou Y, O'Mara K, Berrey MM, Piscitelli SC. Pharmacokinetics and short-term safety of 873140, a novel CCR5 antagonist, in healthy adult subjects. *Antimicrob Agents Chemother* 2005;49(7):2802-6.